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APPLICATION NUMBER:

22-250s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505 (b)(1)
Application Number(s)	22-250
Priority or Standard	Priority
Submit Date(s)	04/22/2009
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Reviewer Name(s)	Kachi Illoh, MD, MPH
Review Completion Date	12/10/2009
Established Name	Fampridine Sustained Release (4-aminopyridine)
(Proposed) Trade Name	
Therapeutic Class	Selective potassium channel blocker
Applicant	Acorda Therapeutics, Inc.
Formulation(s)	Extended Release 10 mg tablets
Dosing Regimen	Single tablet taken orally twice a day
Indication(s)	Improvement of walking ability
Intended Population(s)	Multiple sclerosis patients

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend a complete response. At present, the reviewer is unable to recommend approval of fampridine treatment for the improvement of walking ability in MS patients because the pivotal trials did not clearly show the clinical significance of the small improvement in walking speed with treatment; this is in spite of potential risk for seizures and other neurological adverse events with the drug. So, it remains unclear that the drug's benefits clearly outweigh its risks.

The reviewer recommends the sponsor conducts further clinical trials using smaller than 10 mg doses, with dose adjustment for patients with renal impairment, using appropriate endpoints that may require larger sample sizes. Any additional trials need to be conducted over a longer duration to better assess the seizure risks.

1.2 Risk Benefit Assessment

Fampridine is proposed for an indication that has no previously approved treatment, yet it has potential risks and apparently little clinical benefit. It is associated with a known risk of seizures. In addition, MS relapses and their relationship with treatment were not clearly characterized in the trials. The effect of treatment on EDSS was not shown. Smaller doses than 10 mg of the drug may reduce the potential risks of adverse neurological events and still maintain the drug's efficacy; yet, the sponsor had limited testing of lower drug doses.

The sponsor showed Timed Walk Responder rates were higher with fampridine treatment compared to placebo in both pivotal trials, yet the clinical meaningfulness of the benefit remains unclear. Though more patients on fampridine appear to walk faster, the magnitude of the improvement in walking speed suggests the improvement lacks clinical significance. The responder variable is limited by its ignoring the importance of the extent of improvement in walking speed. So, a small benefit in many patients given the treatment can result in a positive trial even in the absence of a clinically meaningful benefit. Though there is a change in walking speed from baseline with fampridine treatment, the magnitude of the change was not large enough for the average walking speed during treatment to differ from placebo. This suggests the sponsor's responder analysis may not be sensitive enough to determine the clinical usefulness of the treatment.

1.3 Recommendations for Postmarket Risk Management Activities

In the event of approval of fampridine, a risk evaluation and mitigation (REMS) strategy is required. Also, the reviewer agrees with the Clinical Pharmacology review that a dose adjustment will be required for patient with mild and moderate renal impairment.

1.4 Recommendations for Postmarket Studies/Clinical Trials

The reviewer recommends pharmaco-epidemiological surveillance for seizures, MS relapses, and other CNS adverse events if fampridine is approved.

2 Introduction and Regulatory Background

The sponsor presents a clinical development program for fampridine in MS patients. Fampridine is potassium (K+) channel blocker that has no prior approval for any indication. The drug has been compounded in pharmacies and used off-label to improve walking in a number of neurological conditions. There is a concern for seizure risk with the drug. Over the past decade, the sponsor conducted numerous trials in healthy subjects and MS patients. Two trials were conducted under special protocol assessment (SPA). The primary assessment is walking speed responder rates in adult MS patients who are able to walk 25 feet in 8-45 seconds.

2.1 Product Information

Brief description of the product: Fampridine-SR is an extended release form of fampridine that has been evaluated clinically as a treatment for improving neurological function in patients with multiple sclerosis (MS).

Established name: The product's established name is fampridine or 4-aminopyridine. Its proposed trade name was Amaya but recently changed to Ampriva.

Chemical class: Fampridine is an organic compound and belongs to the chemical class of pyridine compounds. It was initially studied in MS patients using the immediate release formulation. Early in its development for MS treatment, two trials (VanDiemen et al., 1993; Bever et al., 1994) examined the relationship of serum levels to side effects and efficacy. The trials suggested that the beneficial effects including motor function were related to total drug exposure whereas toxicity was related to peak serum levels. These results led to the concept of controlled release formulations of 4-AP with the aim of reducing toxicity. Subsequently, a slow release formulation of 4-AP was developed by Elan Pharmeceutical Research Corporation (Athlone, Ireland).

Pharmacological class: Fampridine belongs to the pharmacological class of potassium channel blockers. It is a selective, potassium (K+) channel blocker that is thought to improve conduction of action potential in demyelinated nerves.

Proposed indications, dosing regimens, age group: The proposed indication for Fampridine-SR is the treatment of adult patients with MS for the improvement of walking ability. For this indication it is to be given as 10 mg twice daily.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently no available treatments for the proposed indication of walking disability in patients with multiple sclerosis.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, 4-Aminopyridine, is a pesticide for birds that is registered as Avitrol with the EPA (http://extoxnet.orst.edu/pips/4-aminop.htm). Avitrol repels birds by poisoning a few members of a flock, causing them to become hyperactive. Avitrol is available as grain baits or as a powder concentrate.

(b) (4)

2.4 Important Safety Issues with Consideration to Related Drugs

Fampridine is closely related to 3,4-diaminopyridine (3,4-DAP) that has undergone clinical evaluation in a number of neurological investigations. 3,4-DAP has only been associated with mild symptoms such as digital paraesthesias. Yet, there are major concerns for seizures with the use of fampridine or 3,4-DAP. Generalized tonic-clonic seizures have been documented for this class of agents.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The reviewer obtained information regarding presubmission regulatory activity from the clinical reviews at FDA (Janeth Rouzer, MD and Rob Harris, MD).

Over the years, several small clinical trials of fampridine were conducted in various neurological conditions including spinal cord injury (SCI), Guillain-Barre syndrome, and multiple sclerosis. These trials largely assessed the safety of fampridine. The initial MS trials conducted between 1983 and 1998, were small in size (N<30) and open-label; they tested fampridine in the sustained-release, immediate-release, or parenteral formulations. One of these early trials suggested the safety of concurrent administration of an interferon (Betaseron) and fampridine.

The sponsor evaluated fampridine with MS patients in two phase 2 trials (MS-F201, A Double Blind Dose-Ranging Study of Fampridine-SR in Subjects with Multiple Sclerosis; and MS-F202, Double-Blind, Placebo-Controlled, 20-Week, Parallel Group Study to Evaluate Safety, Tolerability and Activity of Oral Fampridine-SR in Subjects with Multiple Sclerosis). In 2004, the sponsor presented the results of the two trials. Both trials showed statistically significant improvements in leg strength measured with the manual muscle test (LEMMT) and change from baseline in walking speed based on post hoc analysis of the Timed 25 Foot Walk (TW25). The

sponsor also reported a post hoc analysis using responder status, and the preference for the responder status as the primary efficacy variable in future trials.

The responder status assessed consistency of walking speed improvement. A responder was defined as a patient who had faster walking speed for at least three visits (out of a possible 4) during the double-blind period as compared to the maximum value among all five of the non double-blind treatment visits. The Division questioned the clinical significance of results based on the analyses; it noted that the responder criterion was neither validated by that trial nor did it demonstrate maintenance of effect over time. The Division demanded additional validation of the sponsor's outcome measure of responder criterion. The agreements at that meeting were: to conduct a trial to demonstrate effect on two co-primary endpoints, walking speed and a global subjective measure, or have a sequential analysis to validate the clinical meaningfulness of the responder criterion and the maintenance of benefit.

Subsequently, the sponsor proposed another phase 2 trial with prospectively defined responder criterion. It defined a responder, in three steps, as a subject with a faster walking speed for at least three out of four visits during the double-blind treatment period as compared to the maximum speed for any of the pretreatment visits and the first post-treatment visit. The first step required a significantly greater proportion of responders in the fampridine group as compared to the placebo group. This step was thought to demonstrate a meaningful difference between groups in speed. The second step would validate the clinical meaningfulness of the primary efficacy variable by testing whether the responders have a significant improvement in MSWS-12 score, compared to non-responders. MSWS-12 score is a 12-item subjective scale to test whether responders perceive improvement in their walking disability compared to nonresponders during the preceding 2 weeks. In the third step, the fampridine responders must be statistically superior to the placebo group with respect to the endpoint change from baseline (i.e., it must be demonstrated that among subjects who respond to fampridine, the response is maintained). The Division further required the sponsor to justify the inclusion criterion of walking speed in the range of 8-45 seconds and to include a section on concomitants medications in its protocol.

In June 2005, the Division agreed to the sponsor's justification for the walking speed recruitment criterion. The sponsor provided the following information: the normal time for unaffected adults is 4 seconds. The choice of 8 seconds, i.e. a doubling of the normal, as the lower bound allows for sufficient room for treatment-related improvements. The upper bound choice of 60 seconds was based on the earlier trial experience. In the earlier trial MS-F201 that enrolled 27 subjects, two subjects with walking times of over 60 seconds showed great variability from visit to visit with occasional difficulty completing the test walk. In trial MS-F202 that enrolled 211 subjects, subjects with walk times of 45-60 seconds during the screening visit were few (5% of the total) and more likely unable to complete scheduled 25 foot walk (6.3% vs. 0.6% for >45 and <45 seconds respectively). The sponsor suggested that exclusion of the more disabled subjects should help to reduce the variability and increase the reliability of the data collected in MS-F203. The Division agreed to this.

The sponsor's plan included an evaluation of the potential for interaction between concomitant medications and trial endpoints (efficacy and safety measures) within the Statistical Analysis

Plan. With regards to concomitant immunomodulators, the sponsor suggested it was unlikely for any notable interaction because the mechanism of fampridine was not immune function related, and earlier studies showed no interactions. The Division agreed this was an adequate response.

In December 2006, the sponsor discussed the results of the phase 3 trial MS-F203 with the Division; it showed fampridine-SR improved walking ability in MS patients based on the responder analysis. This trial was conducted under a Special Protocol Assessment (SPA). There was an agreement to conduct another phase 3 trial (MS-F204) to confirm the findings.

Trial MS-F204 was very similar to MS-F203 with minor differences. MS-F204 was planned to have shorter treatment duration (8 weeks rather than 14 weeks), equal number of subjects randomized to active and placebo groups, and a fewer outcome measures to focus on the outcomes of interest (walking disability and leg strength). The Division requested the outcomes of secondary endpoints – Ashworth Assessment of spasticity, MSWS-12, SGI, and CGI – be included for additional evaluation of efficacy. And there was no need to demonstrate statistical significance with these secondary endpoints.

In October 2008, the sponsor and the division held a pre-NDA meeting to discuss the results of trial MS-F204 and proposal for NDA submission. The sponsor indicated that in all three well-controlled trials (MS-F202, MS-F203, and MS-F204), treatment with fampridine-SR at 10 mg twice daily resulted in significant increase in the proportion of patients with improvement in walking speed. It added that the secondary endpoints (leg strength, MSWS-12, SGI, and CGI) were also consistent across studies, and benefit was demonstrated across all four MS types. The Division requested additional secondary analyses to include change from baseline at each double-blind visit and at the last visit. These additional analyses required preservation of type 1 error for secondary comparison, and the analyses needed to be conducted for the entire randomized treatment groups (active vs. placebo, not limited to responders).

2.6 Other Relevant Background Information

The sponsor targets walking speed for improvement with fampridine in MS patients with impairment of walking ability. The United States department of Transportation, in its 2003 *Manual on Uniform Traffic Control Devices for Streets and Highways,* recommends a walking speed of 4 ft/second (1.2 m/second) for healthy pedestrians (http://mutcd.fhwa.dot.gov/HTM/2003r1/part4/part4l.htm). Such persons complete the 25-foot walk in 6.25 seconds. The sponsor enrolled in its pivotal trials MS patient with baseline 25-foot walk in 8-45 seconds.

3 Ethics and Good Clinical Practices

The sponsor's submission was of acceptable quality. FDA's inspection by the Division of Scientific Investigations revealed no problems that might affect the integrity of the sponsor's data. Also, the sponsor certified it had no financial arrangement with the clinical investigators.

3.1 Submission Quality and Integrity

In the reviewer's opinion, the quality of the overall submission was acceptable. The information required for the review of fampridine efficacy was easily found. The reviewer did not request for additional datasets, though the statistics reviewer requested additional information.

3.2 Compliance with Good Clinical Practices

The pivotal trials were conducted in compliance with the United States Code of Federal Regulations (CFR) or the international Conference on Harmonization (ICH) Tripartite Guidelines on Good Clinical Practice (GCP) and with the Declaration of Helsinki (October 2006). Informed consent was obtained for each subject. Protocol deviations were catalogued by each site for each trial.

The sponsor conducted meetings with investigators and site visits to ensure understanding of the trial procedures and requirements for data collection. The sponsor also conducted site audit visits to ensure compliance with GCP guidelines.

The sponsor reported protocol deviations in both pivotal trials. In MS-F203, three patients were excluded from the per-protocol analysis due to protocol deviations. Two of the three deviations were randomization errors and the subjects received incorrect treatments in the first two weeks of double-blind period (one fampridine and the other placebo). The sponsor included these 2 deviations as randomized in the analysis. The third deviation was a subject enrolled with abnormal EEG and was subsequently discontinued from trial without completion of walking speed assessments. So, only one subject with protocol deviation was discontinued from the trial. According to the sponsor, the deviations did not affect the interpretation of the results of the trial.

In MS-F204 trial, there were 16 protocol deviations related to eligibility criteria; 9 were randomized to fampridine, 5 to placebo, and 1 was pre-randomization. Deviations led to the exclusion of two patients from the per-protocol analysis. Four deviations led to discontinuation from trial; one discontinuation was at pre-randomization before double blind period, three discontinuations were from non-compliance with protocol (two in fampridine and one in placebo groups). Though more fampridine subjects had major protocol deviations, the sponsor suggested the deviations are unlikely to affect the validity of the efficacy data.

FDA, through its Division of Scientific Investigations, inspected the sponsor and three clinical investigator sites from the two pivotal trials. Please see details of inspection report provided on July 2, 2009, by Dr. Antoine El-Hage. The sponsor was inspected because fampridine is a new molecular entity, while the investigator sites were chosen because they enrolled relatively more patients than other sites. The FDA inspected all four sites (sponsor and three clinical investigators) in the United States between March and May 2009.

The goals of the FDA inspections were validation of submitted data and compliance of trial activities with FDA regulations. The inspected records at the sites included the following: all informed consent forms, source documents, drug accountability records, protocol inclusion and

exclusion criteria, randomization procedures, efficacy end points, and documentation of adverse events.

The inspections of the clinical investigators identified no significant problems to adversely affect data acceptability. Overall, no deviations from regulations were noted at each site inspected. According to the FDA inspections report, the data included in the sponsor's NDA application from the three inspected investigator sites were acceptable.

3.3 Financial Disclosures

The sponsor certified it entered no financial arrangement with the clinical investigators; each investigator had no proprietary interest or significant equity in the sponsor; and no investigator was a recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). In MS-F204 trial, financial disclosure forms were expected from the investigators this year (2009). Of 34 investigators in MS-F203 trial, 18 had their signed financial disclosure follow-up form status received by the sponsor. Two investigators had their unsigned forms received. The sponsor had not received the forms from other investigators despite numerous attempts. In MS-F202 trial, the sponsor received signed financial disclosure forms from eight of fourteen investigators. In MS-F-201 trial, two of four signed financial disclosure forms were received; one investigator was no longer at the site.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please, see details of reviews by respective reviewers of the components of this section.

4.1 Chemistry Manufacturing and Controls

At the time of writing this review, the issue of an impurity (b) (4) in the drug remained unresolved. Please, see review by Dr. Lyudmila Soldatova for a detailed report on this section.

4.2 Clinical Microbiology

None

4.3 Preclinical Pharmacology/Toxicology

Refer reader to non-clinical review.

4.4 Clinical Pharmacology

Fampridine is rapidly absorbed following oral administration. There is no food effect on its bioavailability in the dosage form and it has no obvious interaction with baclofen and beta-

interferon. **PK measurements suggest a need for dose adjustment in MS patients with renal impairment**. The exposure-response relationship indicates lower doses of fampridine have not been substantially evaluated.

4.4.1 Mechanism of Action

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by demyelination and axonal conduction block (Judge and Bever, 2006). Demyelinated PNS nerves continue to conduct action potentials but have conduction block when up to 25-fold increase in internodal conduction time occurs (Rasminsky & Sears, 1972; Bostock & Sears, 1978; Bostock et al, 1978; Judge and Bever, 2006). Myelinated and demyelinated nerves display a wide variety of distribution of Kv channels. Abnormal Kv currents in areas of demyelination decrease action potential duration and amplitude and contribute to conduction failure.

From early experiments, fampridine was shown to increase extracellularly recorded action potential amplitude and duration; also, it slowed action potential repolarization and blocked K+ currents.

Fampridine blocks multiple potassium channels including those found under the myelin sheath in nerve fibers of adult mammals, where they are located primarily in the paranodal and internodal membrane of the axon. Early experiments showed fampridine blocks by binding to the cytoplasmic side of the ion translocation pore in Kv channels.

It is widely believed that fampridine and closely related 3,4-diaminopyridine (3,4-DAP) improve conduction by blocking Kv channels exposed along demyelinated axons or at presynaptic membranes. This belief led to the initial fampridine studies in MS and was largely based on the following experimental observations with 4-AP: restoration of conduction in demyelinated nerves in the peripheral nervous system (PNS); and increase in presynaptic action potential duration and amplitude resulting enhanced transmitter release (Judge and Bever, 2006).

However, more recent observations suggest involvement of other mechanisms. Clinical doses of 4-AP were shown to potentiate synaptic transmission and skeletal muscle twitch tension, but unable to reliably restore conduction in experimentally demyelinated rat dorsal column axons (Smith et al., 2000; Judge and Bever, 2006). Also, clinical studies in MS patients have shown single therapeutic doses of closely related 3,4-DAP did not improve motor conduction time or muscular fatigability while enhancing CNS motor-evoked brain activation. (Fujihara and Miyoshi, 1998; Mainero et al., 2004; and Judge and Bever, 2006). Additional effects attributed to fampridine include immunomodulation due to blockade Kv channels in microglia, macrophages, dendritic cells (DC), and/or T-lymphocytes (Judge et al., 1997; Judge and Bever, 2006).

Both 4-AP and 3,4-DAP are broad-spectrum Kv channel blockers; they block various differentially localized Kv channels to produce their effects. The precise channels at which they produce their different effects are yet to be clearly determined.

4.4.2 Pharmacodynamics

It is proposed that fampridine blocks the potassium channel in demyelinated nerves, thereby reducing the leakage of current from the axon and enhancing action potential conduction. As a result, more impulses are transmitted down the axon. These actions result in transmission of motor impulses between affected brain regions and between brain and spinal cord. The effects of such increased transmission potentially increase activation of lower motor neurons and output to muscle fibers that in turn lead to increased muscle strength, as well as improvements in sensory and coordination functions involved in walking.

4.4.3 Pharmacokinetics

Absorption: After a single 10-mg dose of Fampridine-SR, peak plasma concentration at 3.9 hours following treatment was 25.2 ng/mL. The plasma elimination half-life was 5.5 hours (range, 2.5 to 11.4 hours). Exposure to fampridine increased in a dose-proportional fashion as the doses were increased from 5 mg to 20 mg. Oral administrations of Fampridine-SR tablet result in peak concentrations occurring 3 to 4 hours post-dose in the fasted state and 5 to 6 hours in the fed state. In the fed state, C_{max} was increased by 15% but AUC remained unchanged. The mean apparent elimination half-life is 6 to 8 hours (compared to 3-4 hours in IR-release formulation). The drug does not appear to inhibit or induce human cytochrome P450 enzymes, nor inhibit P-gp substrate. Also, fampridine has been shown to be highly lipid soluble, and it readily crosses the blood brain barrier.

From Fampridine-IR-release studies, the parent drug and its two major metabolites are primarily excreted in the urine. Excretion is primarily renal; with >95% recovered in urine. Renal clearance exceeds glomerular filtration rate, suggesting active tubular secretion. A small amount is metabolized in the liver to 3-hydroxy-4-aminopyridine (primarily by CYP2E1) and subsequently conjugated to 3-hydroxy-4-aminopyridine sulfate. Minimal protein binding occurs (1 to 3%).

Two drug interaction studies with two commonly used drugs in patients with MS (Baclofen and Betaseron) failed to show significant interaction. No interaction was observed with baclofen. Co-administration with immunomodulator MS treatment is important as many of MS patients are expected to be on the treatment: There are suggestions that fampridine and Betaseron can be safely administered together. In December 1999 (12/23/99, final date 03/13/2002), the Agency reviewed results of trial 1194-001US. This trial enrolled 12 MS patients who received single and multiple doses of fampridine-IR at 7.5mg every eight hours with and without concurrent administration of Betaseron. Safety and PK assessments were made during the trial. The results suggested safe co-administration of the two treatments; also, there were no significant differences between the treatments, fampridine alone and combination with Betaseron, both in terms of the C_{max} and AUC. Note that the significance of this trial results are limited. The treatments were co-administered over 4 days, and fampridine-IR was the formulation used. In addition, 3 of enrolled 12 patients withdrew from the trial due to intolerable AEs.

PK measurements suggest a need for dose adjustment in MS patients with renal impairment. C_{max} was increased by 67% in patients with mild renal impairment, 60% in moderate renal impairment, and 100% in severe renal impairment. Similarly, AUC was increased by 75% in mild renal impairment, 105% in moderate, and 299% in severe renal impairment. The sponsor proposes a contra-indication in severe renal failure, and label caution for other patients with renal impairment without offering a dose adjustment.

The exposure-response relationship indicates lower doses of fampridine have not been substantially evaluated. According to the sponsor's analysis, the proportion of responders compared to placebo increased form 25.5% with 10mg, 35.3% with 15 mg, to 42.5% with 20 mg twice daily fampridine. The incidence of CNS AEs was similar between placebo and 10 mg fampridine dose, but increased in a linear exposure-dependent fashion between 10 mg and 20 mg doses.

5 Sources of Clinical Data

A total of 56 clinical studies (table listing below) were conducted in the development of fampridine, of which 19 were in healthy volunteers, 24 in MS patients, 11 in spinal cord injury (SCI), and 2 in Guillain-Barré Syndrome. In these studies, over 1,900 subjects were exposed to fampridine, of which over 1,600 were exposed to the Fampridine-SR formulation. Five of the MS investigations were extension studies that continued from completed trials. Excluding the extension studies, the MS trials enrolled 1,156 subjects.

This review of efficacy focuses more on two adequate and well-controlled phase 3 trials conducted under separate Special Protocol Assessments (SPAs), and to a less extent on a phase 2 dose ranging trial. The two phase 3 trials enrolled 539 subjects with MS to test the proposed indication dose.

5.1 Tables of Studies/Clinical Trials

A listing of the sponsor's studies including trials in MS subjects is provided in the sponsor's table reproduced below. The table also provides the location of the details of each study in the sponsor's submission.

Table 1 Listing of Clinical Studies and Trials (from sponsor's submission)

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
Clinical Trials in Non-Patients						
Open-Label Clinical Trials						
0193-002# 1 Healthy Volunteers	Open-label, single-dose, food effect, crossover 09–Mar-93 14-Mar-93	10 mg FAM-(b)(4) capsule 20 mg q.d., 30 mg and 40 mg b.i.d.	6	6 (100%), 0 — (18, 30) 100% Caucasian	Completed	Module 5.3.1.1
0195-006 1 Healthy Volunteers	Open-label, 2-way crossover 24-Feb-95 09-Mar-95	12.5 mg FAM-(b)(4) (with or without phosphate buffer) Single oral dose	4	4 (100%), 0 35.3 yrs. (16, 40) 100% Caucasian	Completed	Module 5.3.1.1
0494-006# 1 Healthy Volunteers	Open-label, single-dose, 3-way crossover, relative bioavailability 07–June–1994 06–July–1994	12.5 mg FAM-SR tablet, 12.5 mg IR capsule	12	12 (100%), 0 24.4 (18, 32) 100% Caucasian	Completed	Module 5.3.1.1
0497-010# 1 Healthy Volunteers	Open-label, single-dose, 5-way crossover, IVIVC	15 mg FAM-SR tablet, 15 mg FAM-IR tablet 15 mg	12	12 (100%), 0 27.2 (19, 38) —	Completed	Module 5.3.1.1
0791-011# 1 Healthy Volunteers	Open-label, single-dose, food effect, 4-way crossover 1991	5 mg FAM-IR capsule, 20 mg FAM-(b)(4) capsule 20 mg	12	12 (100%), 0 — —	Completed	Module 5.3.1.1

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
0792-001 1 Healthy Volunteers	Open-label, single-dose, randomized, 4-way crossover 22-Feb-93 04-May-93	10 mg FAM-IR 20 mg FAM-(b)(4) Single oral dose	13	13 (100%), 0 29.7 yrs. (25, 33) —	Completed	Module 5.3.1.1
0496-002 1 Healthy Volunteers	Open-label, single-dose 20-Jun-96 23-Jul-96	15 mg ^{14}C FAM solution Single oral dose	4	4 (100%), 0 20.7 yrs. (18, 22) 100% Caucasian	Completed	Module 5.3.3.1
1194-002 1 Healthy Volunteers	Open-label, randomized, 3-way crossover 31-Mar-94 31-May-94	12.5 mg FAM-SR tablet 12.5 mg FAM-SR capsule 12.5 mg FAM-IR capsule Single oral dose	12	12 (100%), 0 27.0 yrs. (23, 35) 100% Caucasian	Completed	Module 5.3.4.1
BE10-25F-SR10OS122003 1 Healthy Volunteers	Open-label, single-dose, randomized, 3-way crossover 04-Dec-03 20-Dec-03	10 mg FAM-SR tablet 25 mg FAM-SR tablet 10 mg FAM solution Single oral dose	30	17 (57%), 13 (43%) 25.4 yrs. (19, 42) 83.3% Caucasian, 6.6% Black, 3.3% European/Middle Eastern, 3.3% Hispanic, 3.3% American Indian	Completed	Module 5.3.1.2
BE10F-SR22004 1 Healthy Volunteers	Open-label, single-dose, randomized, 2-way crossover 16-Mar-04 25-Mar-04	10 mg FAM-SR tablets (from 2 manufacturers, (b)(4) and Elan Corporation) Single oral dose	18	10 (56%), 8 (44%) 29.4 yrs. (20, 45) 100% Caucasian	Completed	Module 5.3.1.2

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
BE25F-SRO22004 1 Healthy Volunteers	Open-label, single-dose, randomized, 2-way crossover 05-Mar-04 14-Mar-04	25 mg FAM-SR tablets (from 2 manufacturers, (b) (4) and Elan Corporation) Single oral dose	22	10 (45%), 12 (55%) 24.2 yrs. (19, 38) 95.5% Caucasian, 4.5% Black	Completed	Module 5.3.1.2
FeFa25F-SR112003 1 Healthy Volunteers	Open-label, single-dose, 2-way crossover 06-Nov-03 15-Nov-03	25 mg FAM-SR tablets Single oral dose	14	5 (36%), 9 (64%) 34.0 yrs. (26, 5) 78.6% Caucasian, 14.3% Asian, 7.1% Black	Completed	Module 5.3.1.2
0593-005 1 Healthy Volunteers	Open-label, randomized, single-dose, 5-period, crossover 08-Nov-93 14-Dec-93	15 mg FAM-IR capsule 15 mg FAM- (b) capsule Single oral dose	10	10 (100%), 0 34.0 yrs. (27, 40) 100% Caucasian	Completed	Module 5.3.1.3
RD10F SR012004 3 15 Patients with Renal Impairment 5 Healthy Volunteers	Open-label, single-dose, non-randomized, 2-stage, parallel group 10-Feb-04 28-Jul-04	10 mg FAM-SR tablets Single oral dose	20	9 (45%), 11 (55%) 60.5 yrs. (19, 80) 75% Caucasian, 25% Black	Completed	Module 5.3.3.3
0194-002 1 Healthy Volunteers	Open-label, single-dose, randomized, 3-way crossover 31-Mar-94 31-May-94	15 mg FAM- (b) 10 mg Baclofen 15 mg FAM- (b) and 10 mg Baclofen Single oral dose	12	13 (100%), 0 29.8 yrs. (18, 40) 100% Caucasian	Completed	Module 5.3.3.4

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
Blinded Clinical Trials						
ELA/G-9101[#] 1 Healthy Volunteer	Double-blind, placebo-controlled, single ascending dose May–1991 June–1991	5 mg FAM-IR capsule up to 25 mg	8	8 (100%), 0 22.6 (20, 26) —	Completed	Module 5.3.3.1
0492-004 1 Healthy Volunteers	Single-blind, randomized, multiple-dose, 4-period, crossover 17-Jun-92 04-Aug-92	20 mg FAM- (b) Oral b.i.d.	14	14 (100%), 0 28.8 yrs. (21, 47) 100% Caucasian	Completed	Module 5.3.4.1
TQTc-F-SR001 1 Healthy Volunteers	Double-blind, placebo-controlled, randomized, double-dummy, parallel group 17-Oct-07 03-Dec-07	10 mg FAM-SR Oral q12h 30 mg FAM-SR Oral q12h Placebo Oral q12h 400 mg Moxifloxacin/ Placebo Oral q12h	208	113 (54%), 95 (46%) 25.0 yrs. (18, 44) 87% Caucasian, 5% Black, 6% American Indian/ Alaskan Native, 2% Asian	Completed	Module 5.3.4.1
Clinical Trials in MS Patients						
Open-Label Clinical Trials						
0195-001US 1 MS Patients	Open-label, single-dose, 3-way crossover Mar-95 Apr-95	12.5 mg FAM-SR tablets Oral 12.5 mg FAM-SR capsules Single oral dose	13	7 (54%), 6 (46%) 47.5 yrs. (30, 60) 92% Caucasian, 8% Asian	Completed	Module 5.3.3.2

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
0296-003US 1 MS Patients	Open-label study 14-May-96 27-Jul-98	12.5 mg FAM-SR tablet 17.5 mg FAM-SR tablet 22.5 mg FAM-SR tablet Oral b.i.d.	20	10 (50%), 10 (50%) 52.0 yrs. (31, 67) 95% Caucasian, 5% Asian	Completed	Module 5.3.3.2
0893-001US 1 MS Patients	Open-label, single-dose, 3-way crossover Mar-93 Dec-93	7.5 and 15 mg FAM-SR capsules Single oral dose	12	6 (50%), 6 (50%) 50.4 yrs. (41,64) 100% Caucasian	Completed	Module 5.3.3.2
1293-001US 1 MS Patients	Open-label, dose escalation 07-Feb-94 13-Apr-94	7.5 mg FAM-SR Oral b.i.d., increased by 2.5 mg b.i.d. weekly	12	6 (50%), 6 (50%) 51.3 yrs. (41, 65) 100% Caucasian	Completed	Module 5.3.3.2
AN751-101 2 MS Patients	Open-label, single-escalating doses 21-Oct-97 21-Jan-98	5 mg FAM-SR 10 mg FAM-SR 15 mg FAM-SR Single oral dose	24	10 (42%), 14 (58%) 45.4 yrs. (29, 56) 100% Caucasian	Completed	Module 5.3.3.2
AN751-102 2 MS Patients	Open-label, multi-center, single treatment period multiple dose study 25-Nov-97 10-Feb-98	20 mg FAM-SR Oral b.i.d. for 13 consecutive days, with a single administration on Day 14	21	10 (48%), 11 (52%) 45.1 yrs. (29, 57) 100% Caucasian	Completed	Module 5.3.3.2

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
Rush 001[#] 1 MS Patients, Healthy Volunteers	Open-label, single-dose pharmacodynamic study 11–Nov–1983 06–Sept–1985	1 to 5 mg i.v. solution 7 to 30 mg	17	17 (100%), 0 34.7 (24, 56) —	Completed	Module 5.3.3.2
1194-001US 1 MS Patients	Open-label, single, and multiple dosing 13-Jan-95 25-Mar-95	7.5 mg FAM-IR capsules Oral 8M units Betaseron IM	12	4 (33%), 8 (67%) 43.8 yrs. (38, 55) 92% Caucasian, 8% Native American	Completed	Module 5.3.3.4
Blinded Clinical Trials						
0293-001US 1 MS Patients (Study terminated prior to planned crossover)	Double-blind, placebo-controlled, 3-period crossover comparison of slow-release fampridine 30 and 40 mg in MS patients 12-May-93 25-Jun-93	30 mg FAM-SR 40 mg FAM-SR Placebo Oral doses administered b.i.d. for 10 days	9	4 (44%), 5 (56%) 50.8 yrs. (41, 58) 100% Caucasian	Terminated early by sponsor	Module 5.3.1.1
MS-F201 4 MS Patients	Double-blind, randomized, placebo-controlled 08-Nov-00 18-Sep-01	5, 10, 15, 20, 25, 30, 35, and 40 mg FAM-SR Placebo Oral doses administered b.i.d. for 8 weeks	36	17 (47%), 19 (53%) 47 yrs. (30, 61) 97% Caucasian, 3% Black	Completed	Module 5.3.5.1

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
MS-F202 24 MS Patients (Adequate/well-controlled study)	Double-blind, placebo-controlled, 20-week, parallel group 27-Feb-03 18-Dec-03	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR Placebo Oral doses administered b.i.d. for 15 weeks	206	75 (36%), 131 (64%) 49.8 yrs. (28, 69) 92% Caucasian, 5% Black, 1.5% Hispanic , 1% Other , 0.5% Asian/ Pacific Islander	Completed	Module 5.3.5.1
MS-F203 33 MS Patients (Adequate/well-controlled study)	Double-blind, randomized, placebo-controlled 07-Jun-05 28-Jun-06	10 mg FAM-SR Placebo Oral doses administered b.i.d. for 14 weeks	300	95 (32%), 205 (68%) 51.4 yrs. (26, 70) 92.7% Caucasian, 4.3% Black, 1.3 % Hispanic, 1.3% Asian/Pacific Islander, 0.3% Other	Completed	Module 5.3.5.1
MS-F204 35 MS Patients (Adequate/well-controlled study)	Double-blind, randomized, placebo-controlled 22-May-07 27-Feb-08	10 mg FAM-SR Placebo Oral doses administered b.i.d. for 9 weeks	239	77 (32%), 162 (68%) 51.7 yrs. (24, 73) 91.2% Caucasian, 5.0% African-American, 1.7% Hispanic, 1.7% Other, 0.4% American Indian/Alaskan Native	Completed	Module 5.3.5.1
MS-F200 1 MS Patients	Double-blind, randomized, placebo-controlled, 4-way, single-ascending dose, crossover 11-Oct-99 11-May-00	5 mg FAM-SR 15 mg FAM-SR 25 mg FAM-SR Placebo Single oral dose	24	8 (33%), 16 (67%) 46.2 yrs. (23, 56) 92% Caucasian, 4% Hispanic, 4% Other	Completed	Module 5.3.1.2

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
1091-001[#] 1 MS Patients	Double-blind, placebo-controlled, 3-period crossover, concentration controlled study 10–Sept–1991 02–Jan–1992	2.5 mg FAM-IR capsule, 5 mg FAM-IR capsule	8	5 (56%), 4 (44%) 47.5 (35, 62) 100% Caucasian	Completed	Module 5.3.3.2
Rush 002[#] 1 MS Patients	Single-blind, placebo-controlled, single-dose 06–Dec–1985 17–Sept–1985	2.5 mg FAM-IR capsule, 5 mg FAM-IR capsule to 25 mg	15	15 (100%), 0 37.2 (25, 48) —	Completed	Module 5.3.3.2
Rush 003[#] 1 MS Patients	Double-blind, placebo-controlled 17–Feb–1987 12–Jan–1989	2.5 mg FAM-IR capsule, 5 mg FAM-IR capsule 7.5 mg to 53.5 mg	17	8 (47%), 9 (53%) 39.8 (28, 53) —	Completed	Module 5.3.3.2
0494-001US 9 MS Patients	Double-blind, randomized, placebo-controlled, parallel group 12-Sep-94 16-Dec-94	12.5, 17.5, and 22.5 mg FAM-SR Placebo Oral doses administered b.i.d. for 6 weeks	161	70 (43%), 91 (57%) 48.9 yrs. (29, 74) 95% Caucasian, 3% African-American, 2% Other	Completed	Module 5.3.4.2
0995-001US 1 MS Patients	Double-blind, placebo-controlled, crossover Sep-95 Nov-95	17.5 mg FAM-SR tablets Placebo Oral doses administered b.i.d. for 1 week/treatment	10	4 (40%), 6 (60%) 48.4 yrs. (33, 57) 100% Caucasian	Completed	Module 5.3.4.2

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
Extension Studies						
0195-001US EXT 1 MS Patients	Open-label extension study 15-Jun-95 22-May-96	12.5 mg FAM-SR tablets Oral b.i.d.	12	7 (58%), 5 (42%) 48.9 yrs. (31, 61) 92% Caucasian, 8% Asian	Completed	Module 5.3.5.2
1293-001US EXT 1 MS Patients	Open-label extension study 14-Mar-94 15-May-96	10-22.5 mg FAM-SR Oral b.i.d., switched from capsule to tablet during extension phase	12	6 (50%), 6 (50%) 51.3 yrs. (41, 65) 100% Caucasian	Completed	Module 5.3.5.2
MS-F202 EXT 21 MS Patients	Open-label extension study 15-Mar-04 (ongoing)	10 mg FAM-SR tablet 15 mg FAM-SR tablet 20 mg FAM-SR tablet Oral	177	66 (37%), 111 (63%) 51.9 yrs. (29, 70) 96.6% Caucasian, 2.3% Hispanic, 1.1% Black	Ongoing	Module 5.3.5.2
MS-F203 EXT 33 MS Patients	Open-label extension study 13-Dec-05 (ongoing)	10 mg FAM-SR tablet Oral b.i.d.	267	87 (33%), 180 (67%) 52.0 yrs. (26, 71) 93.3% Caucasian, 4.1% Black, 1.1% Hispanic, 1.1% Asian/Pacific Islander, 0.4% Other	Ongoing	Module 5.3.5.2
MS-F204 EXT 38 MS Patients	Open-label extension study 27-Aug-07 (ongoing)	10 mg FAM-SR tablet Oral b.i.d. Placebo	239	77 (32%), 162 (68%) 51.7 yrs. (24, 73) 91.2% Caucasian, 5.0% Black, 1.7% Hispanic, 0.4% American Indian/ Alaskan Native, 1.7% Other	Ongoing	Module 5.3.5.2

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
Clinical Trials in SCI Patients						
Open-Label Clinical Trials						
SCI-101 1 SCI Patients	Open-label, escalating dose 24-Mar-98 19-Jun-98	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR Single oral dose	14	9 (64%), 5 (36%) 38 yrs. (17,61) 86% Caucasian, 7% Black, 7% Other	Completed	Module 5.3.5.4
SCI-102 1 SCI Patients	Open-label, escalating dose 24-Mar-98 10-Jul-98	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR Oral b.i.d.	16	14 (88%), 2 (12%) 40 yrs. (22, 59) 100% Caucasian	Completed	Module 5.3.5.4
SCI-103 1 SCI Patients	Open-label, escalating dose 26-Feb-99 30-Jul-99	5 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR 30 mg FAM-SR 35 mg FAM-SR 40 mg FAM-SR b.i.d.	16	13 (81%), 3 (19%) 35.7 yrs. (18, 60) 100% Caucasian	Completed	Module 5.3.5.4
Blinded Clinical Trials						
0295-001US 2 SCI Patients	Double-blind, randomized, placebo-controlled, dose titration, 3-way crossover in chronic SCI patients Sep-95 Jan-96	12.5 mg FAM-SR 17.5 mg FAM-SR Placebo Oral b.i.d. for 1 week	29	28 (97%), 1 (3%) 40.4 yrs. (23, 63) 90% Caucasian, 7% Hispanic, 3% African-American	Completed	Module 5.3.5.4

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
SCI-001 1 SCI Patients	Double-blind, randomized, placebo-controlled 05-Nov-96 23-Dec-96	5 mg FAM-IR Placebo Oral doses administered b.i.d. for 7 days	4	4 (100%), 0 44 yrs. (28, 52) —	Terminated early by sponsor	Module 5.3.5.4
SCI-200 6 SCI Patients	Double-blind, placebo-controlled, escalating dose, crossover in SCI patients 23-Oct-97 28-Apr-98	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR Oral b.i.d. for 1 week	59	49 (82%), 11 (18%) 38.9 yrs. (20, 64) 82% Caucasian, 13% Black, 1.7% Asian, 3.3% Other	Completed	Module 5.3.5.4
SCI-F201 10 SCI Patients	Double-blind, placebo-controlled, parallel group in chronic incomplete SCI patients 27-Jun-00 06-Mar-01	25 mg FAM-SR 40 mg FAM-SR Placebo Oral b.i.d.	91	72 (79%), 19 (21%) 41.5 yrs. (19, 67) 93% Caucasian, 4% Black, 1% Asian, 2% Other	Completed	Module 5.3.5.4
SCI-F203 1 SCI Patients	Double-blind, placebo-controlled, parallel group in chronic complete and incomplete SCI patients 04-Jun-02 29-Oct-03	15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR Oral b.i.d.	9	5 (56%), 4 (44%) 46.0 yrs. (30, 73) 100% Caucasian	Completed	Module 5.3.5.4

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
SCI-F301 51 SCI Patients	Double-blind, placebo-controlled, fixed dose, 2-way crossover 8-Jul-02 16-Feb-04	25 mg FAM-SR Placebo Oral b.i.d.	212	185 (87%), 27 (13%) 40.9 yrs. (17, 70) 82.5% Caucasian, 14% Black, 1% American Indian/ Alaskan Native, 1% Asian, 1.5 % Other	Completed	Module 5.3.5.4
SCI-F302 33 SCI Patients	Double-blind, placebo-controlled, parallel group study in chronic SCI patients 11-Jun-02 14-Nov-03	25 mg FAM-SR Placebo Oral b.i.d.	203	172 (85%), 31 (15%) 40.9 yrs. (18, 73) 88% Caucasian, 9% Black, 0.5% Asian/ Pacific Islander, 2.5% Other	Completed	Module 5.3.5.4
Extension Studies						
SCI-F201 EXT 12 SCI Patients	Open-label, multicenter, extension study 04-Jun-02 07-Jul-04	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR 30 mg FAM-SR 35 mg FAM-SR 40 mg FAM-SR Oral b.i.d.	132	111 (84%), 21 (16%) 42 yrs. (19,68) 93.2% Caucasian, 3.8% Black, 3% Other	Terminated early by sponsor	Module 5.3.5.2
SCI-F300 EXT 40 SCI Patients	Open-label, multicenter, extension study 03-Oct-03 25-Jun-04	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR Oral b.i.d.	230	201 (87%), 29 (13%) 42 yrs. (19,74) 82.2% Caucasian, 15.2% Black, 0.9% American Indian/Alaskan Native, 1.7% Other	Terminated early by sponsor	Module 5.3.5.2

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]	Study Status	Location
Clinical Trials in Guillain-Barre Patients						
Blinded Clinical Trials						
CGBS-2a[#] 1 Guillain-Barre Patients	Double-blind, placebo-controlled, crossover, dose escalation 30–June–1999 01–Dec–1999	5 mg FAM-IR capsules 5 mg to 30 mg daily	8	3 (38%), 5 (62%) 57 (27, 73) 100% Caucasian	Completed	Module 5.3.5.4
CGBS-2b[#] 1 Guillain-Barre Patients	Double-blind, placebo-controlled, crossover, dose escalation 19–Mar–2003 16–Mar–2005	5 mg FAM-IR capsules 5 mg to 30 mg daily	16	11 (69%), 5 (31%) 55.5 (23, 77) —	Completed	Module 5.3.5.4

Differences between Efficacy and Safety Databases

For the purpose of this review, the efficacy database includes MS-F203 and MS-F204 trials, especially the modified intent-to-treat population. The sponsor used an extended pooled analysis database for efficacy by adding a part of MS-F202 (10 mg dose and placebo subjects) trial to the pool of the MS-F203 and MS-F204 trials. In contrast, the safety database included data from healthy subjects and from those with various diseases as MS, SCI, and renal impairment.

No pediatric patients were included in the efficacy database. Despite age limits for trials as low as 18 years, the youngest age enrolled was 24 years.

The overall clinical report is a joint review with input from efficacy, safety, and biometrics reviewers. All the reviewers are jointly responsible for the synthesis and documentation of the overall conclusions for the application review.

5.2 Review Strategy

For the efficacy analysis, we provide an overview of the two pivotal trials (MS-F203 and MS-F204) individually in section 5.3 of this document. We discuss the results of the two trials and pooled analysis in section 6. In contrast to the sponsor's approach, this review did not include MS-F202 trial in the main pooled efficacy analysis because of the following reasons: it was a dose response trial with additional arms evaluating other doses, its efficacy analysis used the responder definition post hoc, and it did not include a category of MS patients (progressive relapsing).

Another different approach used by the reviewer in the pooled analyses was comparing the overall fampridine group to the placebo group, without the differentiation by responder status. The sponsor largely compared three groups – fampridine responders, fampridine non-responders, and placebo. Since the responders were not identified a priori, such responder groups based on the results of the trials are prone to having related variables trend in the same manner. Such a bias can limit the usefulness of the results of the different variables.

5.3 Discussion of Individual Studies/Clinical Trials

MS-F203 "Double-Blind, Placebo-Controlled, 21-Week, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR (10 mg B.I.D.) in Subjects with Multiple Sclerosis" (Final version 1.2; 20 September, 2005)

Design: MS-F203 was a phase 3, multicenter, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of oral Fampridine-SR (10 mg twice daily) in 240 MS subjects. The trial was planned to run over 21weeks consisting of one week pre-screening, two weeks of placebo run-in, **14 weeks of double-blind treatment**, and four weeks of follow-up. Subjects were randomized to one of two treatment groups, Fampridine-SR or placebo, in a 3: 1 ratio. Note, the initial plan changed from a phase 2 to a phase 3 trial in September 2005. Also, the trial enrolled 304 subjects instead of the planned 240.

Protocol:
Summary of inclusion criteria: Subjects with clinically definite MS, aged 18 to 70 years, able to perform two trials of Timed 25 foot Walk within 8-45 seconds at the screening visit.

Summary of exclusion criteria: Female who is either pregnant or breastfeeding, and female of child-bearing potential not on birth control measures; history of seizures or evidence of epileptiform activity on EEG; known allergy to pyridine-containing substances or any of the inactive ingredients of the Fampridine-SR tablet; an investigational drug trial 30 days prior to Screening Visit or plans to enroll in an investigational drug trial at any time during the trial; starting immunomodulatory treatment within 90 days prior to the Screening Visit or any change in the dosing regimen of these drugs within 30 days prior to the Screening Visit; onset of MS exacerbation within 60 days prior to the Screening Visit; corticosteroids treatment within 30 days prior to the Screening Visit or expected to receive regularly scheduled steroid treatments during the trial; cyclophosphainide or mitoxantrone for MS within six months prior to the Screening Visit; any medical condition (including psychiatric disease) that would interfere with the interpretation of the trial results or the conduct of the trial; clinically significant abnormal laboratory values or an abnormal ECG; subject has angina, uncontrolled hypertension, cardiac arrhythmias, or any cardiovascular abnormality judged to be clinically significant by the investigator; subject started a concomitant medication regimen within the preceding three weeks, or their concomitant medication regimen expected to change during the course of the trial; subject with a history of drug or alcohol abuse within the past year; subject previously treated with fampridine; and subject administered botulinum toxin in the lower extremities within 6 months prior to the Screening Visit or expected to receive botulinum toxin in the lower extremities during the trial.

Trial procedure of interest: An ***Evaluator*** performed the Timed 25 Foot Walk test, Ashworth and LEMMT examinations. The evaluator remained blinded to the subject's overall clinical and safety assessments, Clinician Global Impression (CGI) and Subject Global Impression (SGI). An independent ***Clinician*** performed other assessments and had access to the findings of Timed 25 Foot Walk, Ashworth or LEMMT when conducting the CGI. At each visit during double blind treatment, the clinician and evaluator performed the required scales as in table below. **This**

arrangement that allows the clinician access to the findings of the evaluator is a potential source of bias.

Figure 1 MS-F203 Trial Treatment Schedule

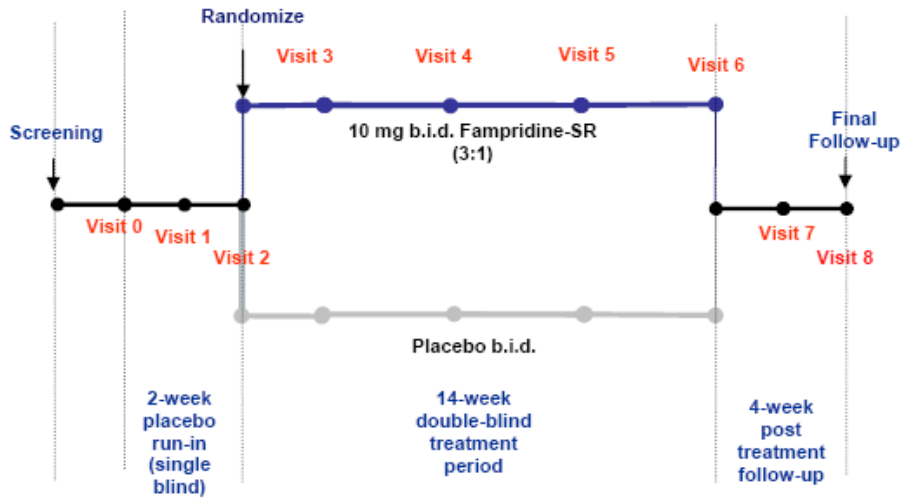

Table 2 Schedule of procedure for MS-F203 (provided in sponsor's protocol)

		2-Week Placebo Run-In		14-Week Randomized Treatment					4-Week No Treatment Follow-up	
Procedure/Drug Dispensed	**Screening Visit**	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/Early Term.[+]**	**Visit 8/Early Term Follow-up.[+]**
Double-Blind Study Day	**-21**	**-14[a]**	**-7[a]**	**0[a]**	**14[a]**	**42[b]**	**70[b]**	**98[b]**	**112[a]**	**126[a]**
Written Informed Consent	C									
Medical and MS Histories	C									
SGI			C	C	C	C	C	C	(C)[≠]	
MSWS-12		C		C	C	C	C	C	C	C
Timed 25 Foot Walk	E	E	E	E	E	E	E	E	E	E
Ashworth	E	E	E	E	E	E	E	E	E	E
LEMMT	E	E	E	E	E	E	E	E	E	E
Physical Exam/Vital Signs	C		C	C	C	C	C	C	C	(C)
Concomitant Meds/Therapy	C	C	C	C	C	C	C	C	C	C
Adverse Events		C	C	C	C	C	C	C	C	C
ECG	C					C		C	(C)[≠]	
EEG	C*								[C][≠*]	
EDSS	C									
Chem/Hem/UA	C					C		C	(C)[≠]	
Urine Pregnancy Test	C							C	(C)[≠]	
PK Serum Analysis		C	C	C	C	C	C	C	C	
Drug Accountability			C	C	C	C	C	C	[C][≠]	
CGI								C	[C][≠]	
SSQ									C	
CSQ									C	
Final Status Assessment										C
Dispense Drug		1 bottle	1 bottle	2 bottle	4 bottles	4 bottles	4 bottles			
Schedule next visit	C	C	C	C	C	C	C	C	C	

C= Assessments obtained by the study Clinician
E= Assessments obtained by the study Evaluator
[a] Visit should take place +/- 1 day. [b] Visit should take place +/- 4 days
*EEG can be performed anytime between Screening Visit and Study Visit 0 (or must be obtained within 30 days prior to the Screening Visit)
[+] Complete all procedures if subject terminates from study early, including those in parentheses; complete all Visit 8 procedures in a two-week follow up.
(C) Complete if necessary (e.g., if clinically significant abnormal value was collected at previous visit). ≠Must be performed if subject terminates early.
C[≠] Only if subject terminates early. [C]*Required only if the subject experienced a seizure while on study.

Endpoints:
Timed 25-Foot walk: At each subject visit, there were two tests of the Timed 25-Foot walk. The Timed 25-Foot walk is derived from the Multiple Sclerosis Functional Composite Score (MSFC). Each test derived walking speed (in feet per second) by dividing 25 feet by the time (in seconds) required to complete the walk. The walking speed for a visit was equal to the average of the walking speeds for the 2 tests walked. The Timed 25 Foot walk was obtained at the screening visit and all subsequent visits.

The 12-Item MS Walking Scale (MSWS-12): This scale assessed the subject's subjective response to questions regarding ability to walk, run, and climb over the preceding 2 weeks. Typically, the total score on MSWS-12 items is transformed to a scale with a range of 0 to 100. High scores indicate greater walking disability.

Ashworth assessment of spasticity: This was used to evaluate the lower extremities for degree of spasticity. Specifically, the evaluator assessed 3 muscle groups (the hip adductors, knee flexors, knee extensors) on a 0-4 scale of spasticity. The Ashworth score is the average of all non-missing assessments. A negative change in Ashworth score signifies improvement in spasticity.

Lower extremity Manual Muscle (LEMMT) Testing: This testing estimated the muscle strength of lower extremities using the modified British Medical Research Council (BMRC) manual muscle testing procedures. It provides estimates of muscle strength bilaterally in four groups of muscles (hip flexors, knee extensors, ankle dorsiflexors, and knee flexors) with scores ranging from 0.0 to 5.0. Higher values indicated better muscle strength. The LEMMT score was the average of all non-missing assessments.

Subject Global Impression (SGI): This was used to evaluate how patient felt on a 7-point scale (from terrible to delight) about the effects of trial medication on the subject's wellbeing over the preceding 7 days.

Clinician Global Impression (CGI): A documentation on a 7-point scale of the clinician's impression of the subjects neurological status on the evaluation date relative to baseline (screening visit). This is highly subject to bias.

Subject Summary Questionnaire (SSQ): This assessed the arm of treatment the subjects believed they were in and their willingness to continue same treatment. SSQ was obtained at visit 7.

Clinician Summary Questionnaire (CSQ): This assessed the arm of treatment the clinicians believed the subjects were in and their willingness to continue subject on the same treatment. CSQ was obtained at visit 7.

The Expanded Disability Status Scale (EDSS) was obtained only at the **Screening Visit** for baseline characterization.

The investigators obtained blood samples at **Visit 0** and at each subsequent visit (except Visit 8) to determine plasma fampridine concentrations.

Analysis:
The trial primary efficacy variable was responder status, based on consistent improvement in walking speed on the Timed 25-Foot Walk. A Timed-Walk Responder was defined as a subject with at least three of the four on-treatment walking speeds faster than the fastest walking speed achieved among five off-treatment visits (i.e., the four pre-treatment visits and the two week post treatment visit).

The sponsor justified the use of responder status variable. Clinicians previously noted a subset of MS patients appeared to respond to fampridine treatment. The selective responsiveness may be related to fampridines's blockade of voltage-dependent potassium channels, resulting in the restoration of conduction of action potential in demyelinated axons. The variability of MS pathology may mean that only a proportion of the patients have axons that are susceptible to fampridine's effects. The sponsor further supported the existence of responder status in MS patients with results of *post hoc* analyses of earlier trials.

Based on the responder status, the sponsor proposed a multi-stage primary endpoint for the MS-F203 trial. The three-stage, stepwise analysis served two purposes: to establish a positive outcome on the primary endpoint, and to establish its clinical meaningfulness with respect to overall walking ability. The ***first step*** was to show a significantly greater proportion of Timed Walk Responders in the Fampridine-SR group as compared to the placebo group. The ***second step*** was to register, irrespective of the treatment allocation, a significant improvement in MSWS-12 score for the Timed Walk Responders when compared to Timed-Walk Non-responders. The ***third step*** was to demonstrate statistically significant improvement in walking speed in fampridine-treated responders compared to the placebo group (responders plus nonresponders) at the last visit on treatment. The sponsor suggested the third step to confirm maintenance of effect by testing whether those patients who responded to Fampridine-SR on the T25FW would still register a significant improvement in walking speed relative to placebo-treated patients at the last observed double-blind visit (i.e., the change from baseline in walking speed at the double-blind endpoint).

The intent-to-treat population was based on all randomized subjects who received treatment and had at least one efficacy (timed 25-foot walk and MSWS-12) evaluation during the double-blind treatment period.

Cochran-Mantel-Haenszel (CMH) test was used to analyze treatment differences in the proportion of responders between fampridine-treated and placebo-treated groups while controlling for center.

The sponsor compared the average change from baseline in the MSWS-12 score over the double blind treatment period between responders and non-responders (i.e. responder status) using an analysis of variance model with effects for responder status and center. The sponsor performed similar analyses for responders compared to non-responders for the secondary subjective variables, average SGI score during the double-blind period and the CGI score recorded at the end of the double-blind period.

The trial secondary efficacy variables were the following:

Objective Secondary Variables

- Percent change from baseline in walking speed at each double-blind visit
- Change from baseline in LEMMT at each double-blind visit
- Change from baseline in the Average Ashworth Score at each double-blind visit

Subjective Variables

- Average SGI score during the double-blind period
- The CGI score, recorded at the end of the double-blind period

In April 2006, the sponsor made changes to the statistical analysis plan (SAP) before breaking the blind (Source MS-F203 Study Report body, section 5.3.5.1.3 of sponsor's submission). The changes are as follows:

- Addition of consistency of improvement in the LEMMT.
- Ordering of secondary endpoints. On meeting the primary endpoint, the secondary endpoints were to be analyzed in the following order:

  1. Fampridine-SR responders had to be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the double-blind period;
  2. Fampridine-SR non-responders had to be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the double-blind period;
  3. Fampridine-SR had to be statistically superior to placebo with respect to the percentage of patients with consistent improvements in LEMMT;
  4. The clinical significance of the consistent improvement in LEMMT was to be validated by demonstrating that patients who had consistent improvements significantly perceive this improvement (via the average SGI score during the double-blind) compared to those who did not;
  5. Fampridine-SR responders had to be statistically superior to the placebo group with respect to the average change from baseline in Ashworth score during the double-blind period;
  6. Fampridine-SR non-responders had to be statistically superior to the placebo group with respect to the average change from baseline in Ashworth score during the double-blind period.

  The secondary subjective variables (SGI, CGI) were not part of the stepwise procedure, but were to serve as additional support to the validation of the responder criteria.

The sponsor added the following clarifications of trial outcome expectations:

Hypotheses to be tested

- The response rate on the primary endpoint for the Fampridine-SR treated patients would be significantly higher than that for the placebo-treated patients;
- The clinical significance of the response criterion would be validated by the MSWS-12, and potentially other subjective measures, comparing responders with nonresponders;
- The walking speed improvement among Fampridine-SR responders, compared to placebo-treated patients, would be maintained at the last treatment visit;

- The Fampridine-SR responders would show a significantly larger improvement in average LEMMT score during the treatment period relative to the placebo-treated group;
- The Fampridine-SR non-responders would not show significant improvement relative to the placebo-treated group with respect to improved walking speed but would show statistically significant improvement on LEMMT;
- An approach equivalent to that of the primary variable, examining consistent improvement in LEMMT would show a higher rate of response in the Fampridine-SR treated patients, compared to the placebo group;
- The consistent improvement criterion for LEMMT was expected to be validated by the SGI, comparing patients with and without consistent improvement in LEMMT;
- The Ashworth score was not expected to show any treatment-related, or responder group effects, based on the lack of a recruitment criterion for spasticity, and the expectation of low Ashworth scores at baseline.

Subject disposition For MS-F203 Trial

MS-F203 trial screened 401 patients from 33 centers in the United States and Canada. The trial enrolled 304 subjects and randomized 301 subjects between June 7, 2005 and June 28, 2006. Of the randomized, 18 (6%) discontinued the trial. One subject discontinued from the placebo group and 17 from the active drug group, as shown in the table below:

Table 3 Disposition of subjects in randomized population MS-F203 trial

Status	Placebo	Fampridine-SR	Total
Randomized Patients	72	229	301
ITT Population	72 (100.0%)	224 (97.8%)	296 (98.3%)
Completed Study	71 (98.6%)	212 (92.6%)	283 (94.0%)
Discontinued Study:	1 (1.4%)	17 (7.4%)	18 (6.0%)
Adverse Event	0 (0%)	11 (4.8%)	11 (3.7%)
Non-Compliance with Protocol	0 (0%)	0 (0%)	0 (0%)
Subject Withdrew Consent	0 (0%)	4 (1.7%)	4 (1.3%)
Subject Lost to Follow-Up	1 (1.4%)	0 (0%)	1 (0.3%)
Other	0 (0%)	2 (0.9%)	2 (0.7%)

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The Per Protocol population included randomized subjects who received trial drug, remained compliant to treatment, and completed all planned assessments of walking speed and MSWS-12. This population (N = 260) included 90.3% (65/72) of the placebo group and 85.2% (195/229) fampridine.

Demographic, Background, and Baseline Variables for MS-F203 Trial

Though MS-F203 trial enrolled 304 subjects, the trial had 300 subjects who received at least one dose of treatment. Of the 300 subjects, 68% (205/300) were females. The ethnic composition was: 92.7% Caucasian, 4.3% Black, 1.3% Hispanic, 1.3% Asian or Pacific Islander, and 0.3% others. The mean age of the subjects was 51.4 years (range 26 to 70 years). There were more

females in the fampridine group (71%, 163/229) compared to placebo (60%, 43/72), but this difference was not significant (p = 0.07). As shown in Table 4 below, there were no differences between the treatment groups in age, ethnicity, MS subtype, EDSS and walking speed, and disease duration. The rate of concomitant drugs used during double blind treatment between the groups was comparable (Table 5 below).

Table 4 Characteristics of subjects in randomized population of MS-F203 trial

Characteristics	**Placebo (N = 72)**	**Fampridine-SR (N = 229)**	**Total (N = 301)**	**P value**
Age (CI) years	51.5 (49.5-53.6)	52.1 (51.0-53.2)	51.4	0.6271
Gender Female %	60 (43/72)	71 (163/229)	301	0.0720
Race %				0.9676
Caucasian	93(67/72)	93 (212/229)	93 (279/301)	
Black	4 (3/72)	4 (10/229)	4 (13/301)	
Hispanic	1 (1/72)	1 (3/229)	1 (4/301)	
Asian/Pacific Islander	1 (1/72)	1 (3/229)	1 (4/301)	
Other	0 (0/72)	<1 (1/229)	<1 (1/301)	
MS Subtype %				0.6502
Primary Progressive	19.4 (14/72)	14.4 (33/229)	15.6 (47/301)	
Progressive Relapsing	2.8 (2/72)	4.4 (10/229)	4.0 (12/301)	
Relapsing Remitting	29.2 (21/72)	27.1 (62/229)	27.6 (83/301)	
Secondary Progressive	48.6 (35/72)	54.2 (124/229)	52.8 (159/301)	
Duration of MS in years	12.7 (10.8-14.6)	13.4 (12.3-14.5)	13.2	0.5326
EDSS at baseline	5.75 (5.52-5.99)	5.76 (5.63-5.90)	5.76	0.9708
Walking Speed at baseline ft/sec (CI)	2.07 (0.09-1.90)	2.06 (0.05-1.96)	2.06	0.9317

Table 5 Concomitant drugs in Safety Population of MS-F203 trial

Characteristics	**Placebo (N = 72)**	**Fampridine-SR (N = 228)**	**Total (N = 300)**
Glatiramer Acetate	25.0 (18/72)	21.9 (50/228)	22.7 (68/300)
Interferons	44.4 (32/72)	43.9 (100/228)	44.0 (132/300)
Glucocorticoids (different formulations)	15.3 (11/72)	11.8 (27/228)	12.7 (38/300
HMG-CoA Reductase Inhibitors	18.1 (13/72)	21.9 (50/228)	21.0 (63/300)

Note inconsistency in table result: Table A.9 of MS-F203 Clinical report presented total interferons for the placebo group as 32 (44.4%). However, there were 9 subjects on Betaseron and 24 listed as interferon beta, giving a total of 33 on interferon. The number also conflicts with the numbers given in table 14.1.6.2 of the Clinical study report in section 5.3.5.1.3 of the sponsor's submission.

Efficacy Variables at Baseline for MS-F203 Trial
There were no differences between the treatment groups with walking speed or other efficacy variables at baseline (table below).

Table 6 Efficacy Variables at Baseline in ITT Population for MS-F203 Trial (Source: Sponsor's submission – Table 7 MS-F203 Clinical Study Report 5.3.5.1.3)

Parameter	Treatment Group: Mean (SD)			
	Placebo N=72	Fampridine-SR N=224	Total N=296	Treatment p-value
Walking Speed (ft/sec)	2.07 (0.711)	2.05 (0.749)	2.06 (0.739)	0.853
LEMMT Score	3.97 (0.737)	4.06 (0.586)	4.04 (0.626)	0.245
Ashworth Score	0.95 (0.670)	0.90 (0.713)	0.91 (0.702)	0.718
MSWS-12 Score	68.48 (22.304)	70.68 (18.551)	70.14 (19.513)	0.472
SGI Score	4.67 (0.939)	4.59 (0.941)*	4.61 (0.939)	0.460

* Two ITT patients did not have a baseline value.

Efficacy Outcome Results
Please see Section 6 (Review of Efficacy) for the outcome results of MS-F203 trial.

MS-F204 "Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR (10 mg b.i.d.) in Patients with Multiple Sclerosis" (Final version 1.3; 10 September, 2007)

The primary objective of MS-F204 was to demonstrate more patients treated with fampridine experienced consistent improvements in walking speed on drug compared to placebo. The secondary objective was to demonstrate improved leg strength in both fampridine responders and non-responders compared to placebo, and measure the maintenance of efficacy towards the end of the dosing interval.

Design: MS-F204 was a phase 3, multicenter, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of oral Fampridine-SR (10 mg twice daily) in 200 MS subjects. The trial was planned to run over 14 weeks consisting of one week pre-screening, two weeks of placebo run-in, **9 weeks of double-blind treatment**, and two weeks of follow-up. Subjects were randomized to one of two treatment groups, Fampridine-SR or placebo, in a 1: 1 ratio.

MS-F204 differed from MS-F203 by the following characteristics of MS-F204: shorter duration of the double-blind treatment period (9 weeks rather than 14); 1:1 randomization to active drug and placebo; and an additional visit at the end of the treatment period to obtain data on efficacy and drug plasma concentration near the end of the dosing interval.

Protocol
The inclusion and exclusion criteria, trial procedures, and assessed endpoints were similar to the MS-F203 trial.

Figure 2 MS-F204 Trial Treatment Schedule

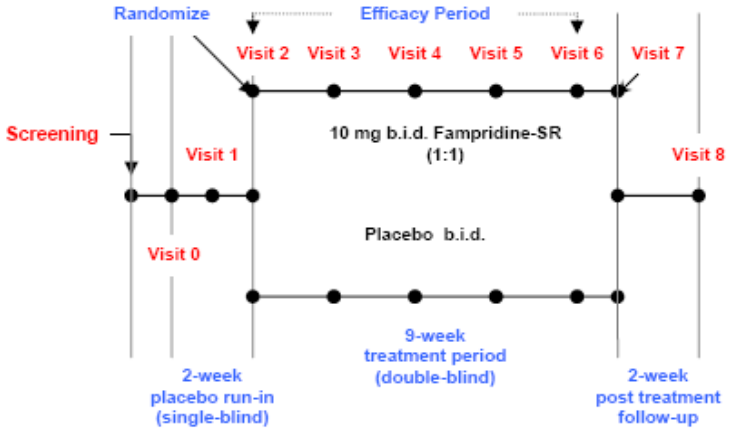

Table 7 Schedule of procedure for MS-F204 (provided in sponsor's protocol)

		2-Week Placebo Run-In		9-Week Randomized Treatment 8-Week Efficacy Period						2-Week Follow-up
Study Procedures[1]	Screening Visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7*	Visit 8/Early Term
Double-Blind Study Day	-21	-14[2]	-7[2]	0[2]	14[2]	28[2]	42[2]	56[2]	63[2]	77[2]
Written Informed Consent	C									
Medical and MS Histories	C									
SGI			C	C	C	C	C	C		C[4]
MSWS-12		C		C	C	C	C	C		C
Timed 25 Foot Walk	E	E	E	E	E	E	E	E	E[7]	E
Ashworth	E	E	E	E	E	E	E	E	E	E
LEMMT	E	E	E	E	E	E	E	E	E	E
Physical Exam/Vital Signs	C		C	C	C	C	C	C	C	C
Concomitant Meds/Therapy	C	C	C	C	C	C	C	C	C	C
Adverse Events		C	C	C	C	C	C	C	C	C
ECG	C					C		C	C	C[4,5]
EEG	C[3]									C[6]
EDSS asssessment	C									
Chem/Hem/UA	C					C		C	C	C[4,5]
Urine Pregnancy Test	C								C	C[4,5]
Fampridine Plasma Sample		C	C	C	C	C	C	C	C	C
Investigational Drug Accountability			C	C	C	C	C	C	C	C[4]
CGI								C		C[4]
SSQ										C
CSQ										C
Final Status Assessment										C
Dispense Investigational drug		1 bottle	1 bottle	2 bottles	2 bottles	2 bottles	2 bottles	1 bottle		
Schedule next visit	C	C	C	C	C	C	C	C	C	

*End of treatment visit, as detailed in Section 5.3.6 of this protocol
C= Assessments obtained by the study Clinician E= Assessments obtained by the study Evaluator
[1] Procedures should be performed (when possible) in the order listed, with the exception of Visit 7 (obtain PK sample immediately after first set of Timed Walk tests, and see Section 5.3.6 of the protocol for the order of other assessments)
[2] Visit should take place +/- 1 day.
[3] EEG can be performed anytime between Screening Visit and Study Visit 0 (or obtained up to 60 days prior to the Screening Visit). EEG results must be reviewed by the Investigator prior to dispensing Visit 0 investigational drug.
[4] Only performed for early termination visits.
[5] For Visit 8, complete assessment only if clinically significant abnormal value was collected at Visit 7.
[6] Required only for early termination visits due to a seizure. [7] This assessment will be performed three times during Visit

Analysis
The efficacy measurements in MS-F204 included the Timed 25 Foot Walk Test and LEMMT. Additional measurements obtained include Ashworth spasticity assessment, MSWS-12, SGI, and CGI.

The primary efficacy variable in MS-F204 was responder status, based on consistency of response in walking speed on the Timed 25 Foot Walk. The secondary efficacy variable was average change from baseline in LEMMT during the eight-week, double-blind treatment period.

Similar to the earlier phase 3 trial, MS-F204 defined a responder as a subject with a faster walking speed for at least three of the first four double-blind visits (Visits 3 through 6) compared to the maximum walking speed for any of the pre-treatment visits (Screening Visit, Visits 0, 1 and 2) and the post-treatment visit (Visit 8). Visit 7 was not included in the responder criterion because the visit's purpose was to obtain data on efficacy and drug plasma concentration near the end of the normal 12 hour dosing interval.

Also, the sponsor conducted a sensitivity analysis of the responder criterion. It considered this analysis as a worst-case scenario sensitivity analysis that defined a modified responder as a responder using the previously outlined definition but with the following restriction: A fampridine-treated subject considered a responder in the primary analysis but who missed the post-treatment visit (Visit 8) was considered a non-responder for the modified responder variable. In this analysis, the restriction did not apply to the placebo group such that a placebo responder in the primary analysis remained a modified responder in the sensitivity analysis even when the patient missed Visit 8.

The plan included the use of Cochran-Mantel-Haenszel (CMH) test to determine differences between the treatment groups in the proportion of walking speed responders, while controlling for center. Differences in the continuous variables were analyzed by t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis group and center.

Results of MS-F204 trial

Subject disposition for MS-F204 Trial
MS-F204 trial screened 362 patients from 35 centers in the United States and Canada. The trial enrolled 240 subjects between May 22, 2007 and February 27, 2008; and randomized 239 subjects. Twelve subjects (5%) discontinued the trial, five from the placebo group and seven from the fampridine group, as shown in the Table 8 below:

Table 8 Disposition of subjects in MS-F204 trial

Status	Placebo	Fampridine-SR	Total
Randomized Patients	119	120	239
ITT Population	118 (99.2%)	119 (99.2%)	237 (99.2%)
Completed Study	114 (95.8%)	113 (94.2%)	227 (95.0%)
Discontinued Study:	5 (4.2%)	7 (5.8%)	12 (5.0%)

Adverse Event	4 (3.4%)	4 (3.3%)	8 (3.3%)
Non-Compliance with Protocol	1 (0.8%)	2 (1.7%)	3 (1.3%)
Subject Withdrew Consent	0 (0%)	0 (0%)	0 (0%)
Subject Lost to Follow-Up	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	1 (0.8%)	1 (0.4%)

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Demographic, Background, and Baseline Variables for MS-F204 Trial

Of the 239 randomized subjects, 68% (162/239) were females. Most of the patients were Caucasian (88%). The mean age of the subjects was 51.7 years (SD, 9.67 years). As shown in Table 9 below, there were no differences between the treatment groups in age, gender, ethnicity, MS subtype, and walking speed, and disease duration. The EDSS score was higher in the fampridine group (p=0.024). Concomitant drug treatment included interferons (35.6%) and glatiramer acetate (23.0%) among others.

Table 9 Characteristics of subjects in randomized population of MS-F204 trial

Characteristics	**Placebo (N = 119)**	**Fampridine-SR (N = 120)**	**Total (N = 239)**	**P value**
Age (SD) years	51.7 (9.83)	51.8 (9.55)	51.7 (9.67)	0.923
Gender Female n (%)	74 (62.2%)	88 (73.3%)	162 (67.8%)	0.077
Race n (%)				0.375
White	105 (88.2%)	113 (94.2%)	218 (91.2%)	
Black	9 (7.6%)	3 (2.5%)	12 (5.0%)	
Hispanic	2 (1.7%)	2 (1.7%)	4 (1.7%)	
American Indian or Alaskan Native	1 (0.8%)	0	1 (0.4%)	
Asian/Pacific Islander	0	0	0	
Other	2 (1.7%)	2 (1.7%)	4 (1.7%)	
MS Subtype n (%)				0.175
Primary Progressive	21 (17.6%)	10 (8.3%)	31 (13.0%)	
Progressive Relapsing	2 (1.7%)	5 (4.2%)	7 (2.9%)	
Relapsing Remitting	40 (33.6%)	43 (35.8%)	83 (34.7%)	
Secondary Progressive	56 (47.1%)	62 (51.7%)	118 (49.4%)	
Duration of MS in years	13.10 (8.69)	14.43 (9.51)	13.76 (9.12)	0.212
EDSS Score at baseline (SD)	5.55 (1.17)	5.83 (0.97)	5.69 (1.09)	0.024
Walking Speed at baseline ft/sec (SD)	2.202 (0.681)	2.117 (0.752)	2.159 (0.717)	0.364

Efficacy Variables at Baseline for MS-F204 Trial

At baseline, there were no differences between the treatment groups with walking speed or LEMMT score. However, the fampridine group had a higher baseline MSWS-12 score as shown in the Table 10 below.

Table 10 Efficacy Variables at Baseline in ITT Population for MS-F204 Trial (Source: Sponsor's submission – Table 10 MS-F204 Clinical Study Report 5.3.5.1.2)

	Treatment Group: Mean (SD)			
Parameter	**Placebo N=118**	**Fampridine-SR N=119**	**Total N=237**	**Treatment p-value**
Walking Speed (ft/sec)	2.202 (0.6812)	2.117 (0.7517)	2.159 (0.7172)	0.364
LEMMT Score	3.962 (0.5803)	3.908 (0.6028)	3.935 (0.5911)	0.457
Ashworth Score	0.800 (0.6722)	0.910 (0.6111)	0.855 (0.6433)	0.258
MSWS-12 Score	67.68 (22.562)	73.80 (17.751)	70.75 (20.478)	0.006
SGI Score	4.36 (0.847)	4.29 (0.877)	4.32 (0.861)	0.508

Efficacy Outcome Results for MS-F204 Trial

Please see Section 6 (Review of Efficacy) for the outcome results of MS-F204 trial.

6 Review of Efficacy

Efficacy Summary

Overall, the sponsor shows Timed Walk Responder rates were higher with fampridine treatment compared to placebo. This result was consistent across the individual trials that constitute the efficacy database and the pooled analysis of the pivotal trials. Though there was a change in walking speed from baseline with fampridine treatment, the magnitude of the change was not large enough for the average walking speed to differ from placebo. This suggests the improvement in walking speed among many treated may not be clinically meaningful. It is important to note that the patients included in the trials were able to walk 25 feet over 8-45 seconds at baseline. Patients with abilities beyond the time limits were excluded. So, there is little information of the benefit of the drug beyond these limits. The sponsor in 2005 alluded to the lack of reliability of the data in more impaired subjects when walking speed exceeded 45 seconds.

6.1 Indication

The proposed indication for Fampridine-SR is for the improvement of walking ability in adult patients with MS.

6.1.1 Methods

The efficacy review is limited, to a large extent, to two pivotal trials (MS-F203 and MS-F204) that prospectively defined the primary endpoint of relevance to the stated indication. Both trials compared a single fixed dose of fampridine (10 mg twice daily) to placebo. The sponsor performed a pooled analysis of three trials (MS-F202, MS-F203 and MS-F204) to show efficacy of fampridine for the stated indication. The overall designs of the two pivotal trials are discussed in more details in Section 5.3 and summarized as modified from the sponsor's table below.

Table 11 Summary of Overall Designs of Trials MS-F203 and MS-F204

Trial, Protocol Name, Design	No. Patients	Double Blind Period	Total Trial Duration	Primary Endpoints	Secondary Endpoints
MS-F203: Double-Blind, Placebo-Controlled, 21-week, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR (10 mg b.i.d.) in Subjects with Multiple Sclerosis Design: Double-blind, randomized, placebo controlled study	304 enrolled 301 randomized (72, placebo; 229, Fampridine-SR)	14 weeks	21 weeks	Prospective primary endpoint, as defined in the SPA: Timed Walk Response, based on the Timed 25 Foot Walk. A responder was defined as a patient who had faster walking speed for at least three of four during the double-blind period as compared to the maximum speed among the first five of the non double-blind (off) treatment visits. Additional requirements of the SPA: Maintenance of effect defined as significantly greater improvement in walking speed at the last double-blind assessment for Fampridine-SR treated Timed Walk Responders compared to placebo treated patients. Validation of Timed Walk Response criterion – statistically significant greater improvement in MSWS-12 score for Timed Walk Responders compared to Timed Walk Non-responders.	Prospective, stepwise analysis of secondary endpoints: • Change from baseline in LEMMT averaged over the double-blind treatment period and compared separately for Timed Walk Responders and Non-responders • Change from baseline in the Average Ashworth Score over the double-blind treatment period, and compared separately for Timed Walk Responders and Non-responders.

MS-F204: Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR (10 mg b.i.d.) in Patients with Multiple Sclerosis Design: Double-blind, randomized, placebo controlled study	240 enrolled 239 randomized (119, placebo; 120, Fampridine-SR)	9 weeks	14 weeks	Prospective primary endpoint, as defined in the SPA: Timed Walk Response, based on the Timed 25 Foot Walk. A responder was defined as a patient who had faster walking speed for at least three of the first four visits during the double-blind period as compared to the maximum speed among all five of the non double-blind (off) treatment visits.	Prospective secondary endpoint: Average change from baseline in LEMMT during the eight-week, double-blind treatment period, comparing Timed Walk Responders and Timed Walk Non-responders separately and sequentially against placebo treated patients. Pharmacokinetic data was to be collected at an additional fifth double-blind treatment visit (Visit7) that was not part of the overall efficacy analysis. Additional assessments, including MSWS-12, SGI, CGI and Ashworth score, were collected for purposes of a pooled analysis with other studies and were not formal secondary endpoints.

Note: MSWS-12 = The 12 Item Multiple Sclerosis Walking Scale; SGI = Subject Global Impression; CGI = Clinician Global Impression; LEMMT = Lower Extremity Manual Muscle Test

The third trial included in the sponsor's pooled analysis is shown below.

Table 12 Overall Design of MS-F202 Trial

			Study Duration (weeks)		Study Endpoints	
Study No., Protocol Name, Design	No. Patients	Dose, Regimen Route	Double Blind Period	Total Study	Primary	Secondary
MS-F202: Double-Blind, Placebo-Controlled, 20-Week, Parallel Group Study to Evaluate Safety, Tolerability and Activity of Oral Fampridine-SR in Patients with Multiple Sclerosis *Design:* Double-blind, randomized, placebo controlled, dose comparison study	211 enrolled 206 Randomized (47, placebo; 52, 10 mg b.i.d. 50, 15 mg b.i.d. 57, 20 mg b.i.d. Fampridine-SR)	FAM-SR Tab; 10, 15, 20 mg; b.i.d.; Oral	15 weeks	20 weeks	*Prospective primary endpoint:* percent change from baseline in average walking speed measured using the Timed 25-Foot Walk *Post hoc responder analysis:* Consistency of walking speed improvement (Timed Walk Response). A responder was defined as a patient who had faster walking speed for at least three of four during the double-blind period as compared to the maximum speed among all five of the non double-blind (off) treatment visits.	*Prospective secondary endpoints:* a response criterion based on an average improvement of >20% in walking speed during the double-blind treatment period; average improvement in Lower Extremity Manual Muscle Test (LEMMT) score and 9-Hole Peg; Paced Auditory Serial Addition Test scores (both from the MS Functional Composite - MSFC); the MSFC combined score; spasticity assessment (Ashworth Score); Clinician's Global Impression of Change (CGI); Subject's Global Impression (SGI); the 12-Item MS Walking Scale (MSWS-12); and the Multiple Sclerosis Quality of Life Inventory (MSQLI).

Both pivotal trials (MS-F203 and MS-F204) had similar inclusion and exclusion criteria. They enrolled adult clinically definite MS subjects, able to perform two trials of Timed 25 foot Walk within 8-45 seconds at the screening visit. Included among a host of exclusion criteria were: female pregnant or breastfeeding subjects; and history of seizures or evidence of epileptiform activity on EEG.

6.1.2 Demographics of Pooled Analysis of MS-F203 and MS-F204 Trials

Demographics for the individual trials are presented in Section 5.3 of this review, while that for the pooled analysis is presented in this section. Of the 540 randomized subjects, 368 (68%) were females. As in the individual trials described in section 5, most of the subjects were Caucasian (92%). The mean age of the subjects was 52 years (SD, 9 years) with average disease duration of at least 13 years.

There were imbalances between the treatment groups at baseline. As shown in Table 13 below, there were no differences at baseline between the treatment groups in age, proportion of ethnic groups, MS subtype, median EDSS score, walking speed, LEMMT, and disease duration. However, there were imbalances between the groups in gender, height, weight, and MSWS-12 score. There were fewer females (p=0.011) in the placebo group (61%) compared to the fampridine group (72%).

Table 13 Characteristics of Subjects in Pooled Efficacy Randomized Population

Characteristics	Placebo (N = 191)	Fampridine-SR (N = 349)	Total (N = 540)	P value
Age (SE, standard error) years	51.6 (0.67)	52.0 (0.49)	51.9 (0.40)	0.664

Gender Female n (%)	117 (61.3%)	251 (71.9%)	368 (68.2%)	0.011
Race n (%)				0.640
White	172 (90.1%)	325 (93.1%)	497 (92.0%)	
Black	12 (6.3%)	13 (3.7%)	25 (4.6%)	
Hispanic	4 (2.1%)	6 (1.7%)	10 (1.9%)	
American Indian or Alaskan Native	1 (0.8%)	0	1 (0.4%)	
Asian/Pacific Islander	1 (0.5%)	3 (0.9%)	4 (0.7%)	
Other	2 (1.1%)	2 (0.6%)	4 (0.7%)	
Height in cm (SE)	169.6 (0.70)	167.9 (0.52)	168.6 (0.42)	0.0483
Weight in kg (SE)	78.6 (1.36)	74.8 (1.00)	76.1 (0.82)	0.0225
Body Mass Index (SE)	27.3 (0.44)	26.5 (0.33)	26.8 (0.26)	0.1078
MS Subtype n (%)				0.128
Primary Progressive	35 (18.3%)	43 (12.3%)	78 (14.4%)	
Progressive Relapsing	4 (2.1%)	15 (4.3%)	19 (3.5%)	
Relapsing Remitting	61 (31.9%)	105 (30.1%)	166 (30.7%)	
Secondary Progressive	91 (47.6%)	62 (51.7%)	186 (53.3%)	
Duration of MS in years (SE)	13.05 (0.63)	13.80 (0.47)	13.64 (0.38)	0.332
EDSS Score median (IQL)	6.0 (3.5-6.5)	6.0 (6.0-6.5)	6.0 (6.0-6.5)	0.254
Walking Speed at baseline ft/sec (SE)	2.15 (0.05)	2.08 (0.04)	2.10 (0.03)	0.285
LEMMT at baseline (SE)	3.96 (0.04)	4.01 (0.03)	3.99 (0.03)	0.356
MSWS-12 at baseline (SE)	67.85 (1.44)	71.67 (1.06)	70.41 (0.86)	0.033
Ashworth score (SE)	0.86 (0.05)	0.89 (0.04)	0.89 (0.03)	0.554
SGI score (SE)	4.48 (0.05)	4.48 (0.05)	4.48 (0.04)	0.979

6.1.3 Subject Disposition of Pooled Analysis of MS-F203 and MS-F204 Trials

Both efficacy trials screened a total of 763 subjects, enrolled 544, and randomized 540 subjects. Of the subjects screened, 29% failed screening. Thirty subjects (6%) of the randomized discontinued the trials; 24 were in the fampridine group and 6 in the placebo group. The reasons for screen failures were not stated clearly in the sponsor's submission.

Table 14 Disposition of subjects in Pooled MS-F204 and MS-F204 trials

Status	**Placebo**	**Fampridine-SR**	**Total**
Randomized Patients	191	349	540
ITT Population	190 (99.5%)	343 (98.3%)	533 (98.7%)
Completed Study	185 (96.9%)	325 (93.1%)	510 (94.4%)
Discontinued Study:	6 (3.1%)	24 (6.9%)	30 (5.6%)
Adverse Event	4 (2.1%)	15 (4.3%)	19 (3.5%)
Non-Compliance with Protocol	1 (0.5%)	2 (0.6%)	3 (0.6%)
Subject Withdrew Consent	0 (0%)	4 (1.2%)	4 (0.7%)
Subject Lost to Follow-Up	1(0.5%)	0 (0%)	1 (0.2%)
Other	0 (0%)	3 (0.9%)	3 (0.6%)

6.1.4 Analysis of Primary Endpoint(s)

Primary Endpoints for MS-F203 Trial

Responder Status Rates Between Treatment Groups

The responder rate was higher in the fampridine group compared to placebo. The primary efficacy variable was responder status, based on consistent improvement in walking speed on the Timed 25-Foot Walk. This section analysis used the ITT population (N = 296). The responder rate in the fampridine group was 34.8% (78/224), and in the placebo group 8.3% (6/72); the difference was significant between the treatment groups ($p < 0.001$). Interestingly, the results closely reflect the predictions from the protocol's sample size calculation. The protocol power calculation predicted responder rates of 35.3% for fampridine and 8.5% for placebo with a sample size of 240 subjects. Regardless, the fampridine group achieved a higher proportion of responder status compared to placebo.

Treatment Groups by Responder Status

The subjects grouped by responder status in treatment arms are as follows: placebo responders (N = 6), placebo non-responders (N = 66), fampridine responders (N = 78), fampridine non-responders (N = 146). According to the pre-specified analysis plan, the sponsor largely compared the placebo group (responders and non-responders) to the fampridine responders in the ITT population.

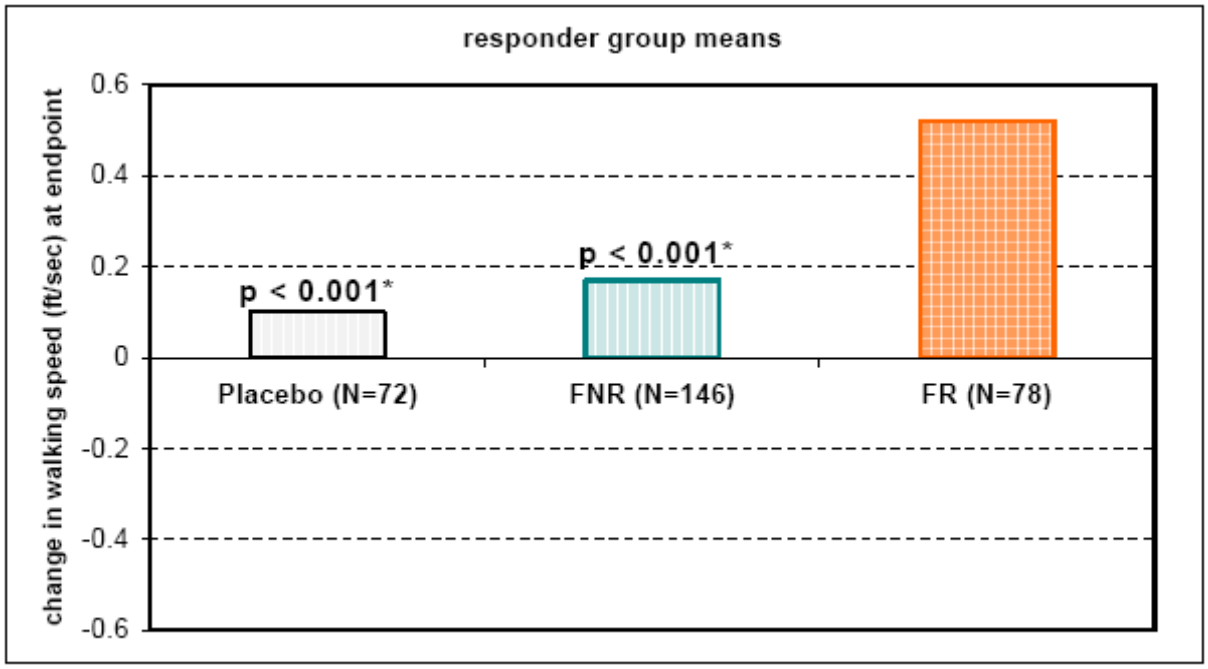
MSWS-12 Score in Timed Walk Responders and Non-responders

The sponsor reported a significant improvement in the 12-Item MS Walking Scale (MSWS-12) for walking responders compared to non-responders. MSWS-12 assessed a patient's subjective response to questions regarding ability to walk, run, and climb over the preceding 2 weeks. The sponsor compared the 84 responders (78 in the Fampridine-SR group and 6 in the placebo group) against the 212 non-responders (146 in the Fampridine-SR group and 66 in the placebo group) on the average change from baseline in MSWS-12 to determine if patients with consistently improved walking speeds could perceive benefit relative to those patients who did not. For the comparison, the sponsor performed an analysis of variance model with effects for responder status and center. The average change from baseline in MSWS-12 was -6.84 (standard deviation, SD of 12.97) in the fampridine responders compared to 0.05 (SD, 11.25) in the non-responder group ($p<0.001$). These MSWS-12 results suggested the responders' had greater improvements in their ability to walk, run, and climb. The sponsor indicated that MSWS-12 results establish the clinical meaningfulness of walking speed response with respect to overall walking ability.

Maintenance of Walking Speed Improvement at Last Treatment Visit in Fampridine Responders

The sponsor reported maintenance of walking speed improvement to the last treatment visit by fampridine responders. The mean changes in walking speed at the double-blind endpoint from baseline were 0.10 ft/sec for the placebo group and 0.53 ft/sec for the fampridine responder group. The corresponding change in walking speed for fampridine non-responder was 0.17 ft/sec (as shown in Figure 3 below). The difference between the fampridine responder and placebo groups was significant ($p < 0.001$).

Figure 3 Change from Baseline in Walking Speed at the Double-Blind Endpoint (Source: Sponsor's Figure 4 in MS-F203 Clinical Study Report 5.3.5.1.3)



ABBREVIATIONS: FNR=Fampridine-SR non-responders; FR=Fampridine-SR responders
*: p-value versus Fampridine-SR responder group; p=0.483 for the other comparison (FNR vs. placebo).

The sponsor reported that all three components of the multi-stage primary endpoint for the trial were successfully achieved.

Primary Efficacy Endpoint in MS-F204 Trial
As in MS-F203 trial, the primary efficacy variable for MS-F204 trial was responder status, based on consistency of response in walking speed on the Timed 25 Foot Walk

Responder Status Rates Between Treatment Groups
The responder rate was higher in the fampridine group compared to placebo. The difference in responder rate, between the fampridine group 42.9% (51/119) and the placebo group 9.3% (11/118), was significant (p <0.001). Though not a part of the primary analysis, the mean change in walking speed during the double-blind period ranged from 21.45% to 26.80% for fampridine responders compared to 7.07% to 8.78% for the placebo group at every visit.

Treatment Groups by Responder Status
The subjects were grouped into the following treatment groups: placebo responders (N =11), placebo non-responders (N = 107), fampridine responders (N = 51), fampridine non-responders (N = 68). In the same manner as the MS-F203 trial, MS-F204 compared the placebo group (responders and non-responders) to the fampridine responders in the ITT population.

Primary Efficacy Endpoint of Pooled Analysis of MS-F203 and MS-F204 Trials

The same primary efficacy variable for both phase 3 trials was used in this pooled efficacy analysis. The variable is Timed Walk Responder status, based on consistent improvement in walking speed on the T25FW. A Timed Walk Responder was defined as a patient with a faster walking speed on this test for at least three of the four (efficacy) visits during the double-blind treatment period, as compared to the maximum walking speed achieved among any of the four pre-treatment visits and the two week-post treatment visit. The sponsor analyzed the primary efficacy variable by comparing the proportion of responders in the treatment groups.

Problems exist with the use of the sponsor's primary endpoint. It has not been frequently used as a primary endpoint in MS clinical trials of other drugs. In MS patients, it is not clear what degree of improvement in walking speed improves walking ability or quality of life. In general, useful endpoints in trials include a clinically significant measure of quality of life or disability reduction. However, the sponsor used a primary endpoint that is a response (or intermediate) variable. The responder variable ignores the importance of the extent of improvement in walking speed. So, a small benefit in many patients receiving the active drug will result in a positive trial, even when the benefit is not clinically significant or meaningful for the patient. Statistical significance can be achieved without clear clinical significance. Supportive endpoints such as EDSS are potentially helpful, especially when MSWS-12 is not clearly validated by the Agency for MS trials. Only baseline EDSS was performed in the sponsor's trials.

The overall design of the trials appears appropriate to test the efficacy of fampridine in MS patients with walking disability. However, limitations exist in the lack of a more elaborate dose finding. With the risk of seizures in doses close to the tested and absence of an increase in efficacy with the higher doses, lower doses ought to be tested. Also, the sponsor emphasizes the presence of clear responders with fampridine treatment. An attempt at identifying the responders a priori will facilitate an enrichment design to target the patients most likely to benefit from the treatment. Yet, the two trials in the pooled efficacy analysis meet the conditions for adequate and well-controlled trials; this assessment is based on adequacy of blinding, randomization, prospective statistical analytic plan. A limiting factor of the trial is the inclusion of only patients able to perform two trials of Timed 25 foot Walk within 8-45 seconds. It is difficult to extrapolate the findings of the trial results to patients who have walking disability but are unable perform at the set time limits at baseline. Thus the finding of drug efficacy does not confer effectiveness for all MS patients with walking disability.

Responder Status Rates between Treatment Groups in Pooled Analysis
As with the individual trials, the pooled analysis responder rate was higher in the fampridine group compared to placebo. The primary efficacy variable was responder status, based on consistent improvement in walking speed on the Timed 25-Foot Walk. The responder rate in the fampridine group was 37.6% (129/343), and in the placebo group 9.0% (17/190); the difference was significant between the treatment groups ($p < 0.001$).

Treatment Groups by Responder Status in Pooled Analysis
The subjects were grouped into the following treatment groups: placebo responders (N = 17), placebo non-responders (N = 173), fampridine responders (N = 129), fampridine non-responders (N = 214).

The reviewer performed an analysis of the modified walking speed responder, and arrived at the same conclusion. The modified walking speed responder supposes the worst-case-scenario that assigns a responder in the fampridine group with a missing visit to the non-responder group. This yielded 37.0% (127/343) responders in the fampridine group to 9.0% (17/190) placebo (p <0.001). On mixed models analysis using modified walking speed responder status, only treatment arm (fampridine) significantly predicted odds of response (p=0.001). The odds of response were not predicted by the other covariates: walking speed at baseline (p=0.388), height (0.570), weight (p=0.177), MSWS-12 at baseline (p=0.813), and gender (0.866).

The sponsor suggested that MSWS-12 validates timed walk response as a clinically meaningful endpoint. The sponsor makes the case for MSWS-12 results being a useful validation for the time walk response. The change in MSWS-12 ranged between -6.04 to -11.79 for responders in the individual and pooled analyses compared to 0.85 to -2.49 in non-responders (all p=0.001). With respect to treatment group differences, the reviewer obtained from the pooled analysis, a change from baseline MSWS-12 of -2.69 (CI, -3.95 to -1.42) for fampridine treatment compared to 0.69 (CI, -1.001 to 2.39) for placebo (p=0.0018). However, the average MSWS-12 score during the double-blind treatment was not different between treatment groups (p=0.8348).

The sponsor showed maintenance of time walk response in fampridine responders during treatment. The sponsor showed significant differences in the change from baseline in walking speed at the end of double-blind treatment for fampridine responders compared to non-responders and placebo (all p<0.001).

In the reviewer's pooled analysis of the whole groups (disregarding responder status) fampridine treatment was associated with improvement in walking speed from baseline to the end of double blind treatment. The change from baseline in walking speed at the end of double-blind treatment was 0.30 ft/sec for fampridine and 0.15 ft/sec for placebo (p=0.0016). Note that despite the significant change, **the walking speed at the end of double-blind treatment was not different between the treatment groups** (2.37 ft/sec versus 2.30 ft/sec, p=0.4269), suggesting that the magnitude of change is small.

In the average change during double blind treatment from baseline in walking speed, the sponsor showed significant improvement with fampridine responders compared to non-responders and placebo. In my pooled analysis, the average change from baseline in walking speed was improved (p<0.001) in the fampridine group (0.29 ft/sec) over placebo (0.14 ft/sec). Again discounting responder status, the average walking speed during treatment is not different between treatment groups (2.36 ft/sec versus 2.29 ft/sec, p=0.3825).

To determine the variables that predicted the change from baseline in walking speed, the reviewer performed two mixed models analyses. In the first, the response (dependent) variable was change from baseline in double blind walking speed; the independent variables adjusted for were baseline walking speed, treatment arm, height, weight, and baseline MSWS-12 score. Only baseline walking speed (p<0.001) and fampridine treatment (p<0.001) were predictive of change in walking speed from baseline in the pooled efficacy population. In second mixed models

analysis that excluded treatment arm, only baseline walking speed predicted change in walking speed (p=0.0015) while the following variables did not predict the change: center, gender, MS subtype, and EDSS. This suggests that among the variables examined a subject's baseline walking speed and fampridine treatment contribute to the subject's improvement in walking speed.

6.1.5 Analysis of Secondary Endpoints

Secondary Endpoints of MS-F203 Trial

Average percent change from baseline walking speed in MS-F203 Trial

The average percent change from baseline walking speed to the double-blind period was higher in the fampridine responders group compared to placebo. The mean (SD) change from baseline in walking speed was 0.51 (SD, 0.43) ft/sec for fampridine responders, 0.16 (SD, 0.31) for fampridine non-responders, and 0.10 (SD, 0.29) for placebo. The difference between placebo and fampridine non-responders in average change from baseline (p=0.297) or percent change from baseline in walking speed (p=0.335) was not significant. The average improvement (percent change from baseline) in walking speed for the fampridine responders group during the double-blind period was 25.2% (SD, 16.2%) compared to 4.7% (SD, 15.7) for the placebo group (p<0.001). The average percent change for the fampridine responders group during the double-blind period ranged from 24.2% to 26.1% compared to 2.1% to 7.4% for the placebo group (p<0.001 at every visit).

Lower extremity Manual Muscle (LEMMT) Testing in MS-F203 Trial

The fampridine responders showed better improvements in LEMMT score that estimated the lower extremities muscle strength. The average improvement in the LEMMT scores for the fampridine responders was 0.18 (SD, 0.19) compared to 0.04 (SD, 0.22) for placebo (p<0.001). The average improvement in the LEMMT scores for the fampridine non-responders was 0.11 (SD, 0.21), which was a better improvement compared to placebo (p=0.046). The LEMMT score improvement for the fampridine responders group during the double-blind period ranged from 0.16 to 0.20 compared to 0.03 to 0.05 for the placebo group at every visit. The difference between the treatment groups was significant at each visit (p<0.01) except at the last visit (p=0.07). Note that the sponsor was unsuccessful at validating the clinical significance of LEMMT variable, when it showed no significant differences in SGI between subjects with and those without consistent improvements in LEMMT (p=0.808).

Ashworth assessment of spasticity in MS-F203 Trial

There was no significant change in the Ashworth assessment of spasticity with fampridine treatment. A reduction from baseline in the Ashworth score suggests improvement. The average reduction from baseline in the Ashworth score was 0.13 for the fampridine responders, 0.17 for fampridine non-responders, and 0.07 for the placebo group. The difference between the placebo group and the fampridine responders was not significant (p=0.09). Following the stepwise analytical procedure for evaluation of secondary endpoints, the difference in the Ashworth assessments between the fampridine non-responders and placebo (p=0.024) was technically not significant.

Subject Global Impression (SGI) and Clinician Global Impression (CGI) in MS-F203 Trial
These variables were not part of the prespecified secondary analyses, but the sponsor included SGI and CGI variables to bolster its argument for the clinical meaningfulness of the walking speed responder criterion. The sponsor showed both variables were scored higher in the walking speed responders compared to non-responders ($p<0.001$).

Secondary efficacy Endpoint in MS-F204 Trial
The secondary efficacy variable in MS-F204 Trial was average change from baseline in LEMMT during the eight-week, double-blind treatment period.

Lower extremity Manual Muscle (LEMMT) Testing in MS-F204 Trial
The fampridine responders showed better improvements in LEMMT score that estimated the lower extremities muscle strength. The average improvement in the LEMMT scores for the fampridine responders was 0.15 (SD, 0.21) compared to 0.04 (SD, 0.25) for placebo ($p=0.028$). The average improvement in the LEMMT scores of 0.05 (SD, 0.22) for the fampridine non-responders was not different from the placebo group ($p=0.600$) or from the fampridine responders ($p=0.134$). The LEMMT score improvement for the fampridine responders group during the double-blind period ranged from 0.09 to 0.18 compared to 0.02 to 0.07 for the placebo group at every visit.

In the reviewer's analysis, there was no difference clinically in leg strength between the overall treatment groups in MS-F204. The average improvement in LEMMT for the overall fampridine group during the double-blind period was 0.09 (CI, 0.05-0.13) units compared to 0.04 (CI, -0.001 to 0.085) units for the placebo group ($p=0.125$). The average improvement from baseline in LEMMT for the overall fampridine group at the last observed double-blind visit was 0.10 (CI, 0.04-0.16) units compared to 0.07 (CI, 0.01-0.13) units for the placebo group ($p=0.406$). The average LEMMT for the overall fampridine group during the double-blind period was 4.00 (CI, 3.89-4.11) compared to 4.00 (CI, 3.90-4.11) for the placebo group ($p=0.927$). Likewise, the average LEMMT for the overall fampridine group at the last observed double-blind period was 3.91 (CI, 3.8-4.01) compared to 3.96 (CI, 3.86-4.07) for the placebo group ($p=0.478$). These results indicate there was no change clinically in the leg strength between treatment groups for this trial.

Secondary Endpoint of Pooled Analysis of MS-F203 and MS-F204

LEMMT Testing in Pooled Analysis of MS-F203 MS-F204 Trial
The fampridine group showed better results on the secondary efficacy variable used for both phase 3 trials, average improvement in LEMMT. In the pooled results conducted by the sponsor, the average improvement in LEMMT for fampridine responders during the double-blind period was 0.16 units compared to 0.03 units for the placebo group ($p<0.001$).

In the reviewer's pooled analysis, the average improvement in LEMMT for the overall fampridine group (irrespective of responder status) during the double-blind period was 0.12 units compared to 0.04 units for the placebo group ($p=0.0002$). Also, the average LEMMT for the

overall fampridine group (irrespective of responder status) during the double-blind period was 4.12 units compared to 4.01 units for the placebo group (p=0.0307).

The results, from combining both pivotal trials, indicate that there was a statistically significant improvement in leg strength with fampridine treatment. However, the magnitude of the improvement is so small as to question its clinical significance. On the LEMMT scale, the average score for both treatment groups fall under the same degree of leg strength (level 4), which is voluntary movement against moderate resistance applied by the examiner. The variability of moderate resistance obtainable by different examiners further limits the usefulness of small improvement in length strength as observed with the fampridine group.

6.1.6 Other Endpoints

Other Endpoints in MS-F203 Trial

Efficacy Endpoints at Follow-up in MS-F203 Trial

At the last follow-up visit when the subjects were four weeks from end of double blind treatment, there no differences in walking speed (p=0.802), LEMMT (p=0.607), or Ashworth score (p=0.587) between the fampridine responders or placebo.

Adjustment for Covariates in MS-F203 Trial

There were no significant differences between the treatment groups in terms of demographics and other baseline characteristics. The sponsor reported further analysis, adjusted for center and gender, and came to the same conclusion in favor of fampridine.

Analyses of Per Protocol Population in MS-F203 Trial

The conclusions from the analysis of the per protocol population were supportive of the primary analysis. The responders were 9.2% (6/65) for placebo and 35.4% (65/195) for fampridine treatment (p<0.001).

Reviewer's Additional Efficacy Results of ITT analysis in MS-F203

At baseline, average walking speed was not different (p=0.8990) between fampridine (2.05 ft/sec; CI, 1.96-2.15) compared to placebo (2.06 ft/sec; CI, 1.86-2.34)

The average walking speed during the double-blind treatment **was not different** (p=0.1527) between fampridine (2.34 ft/sec; CI, 2.22-2.46) compared to placebo (2.16 ft/sec; CI, 1.95-2.37). Likewise, the walking speed at the end of the double-blind treatment **was not different** (p=0.1709) between fampridine (2.35 ft/sec; CI, 2.22-2.48) compared to placebo (2.16 ft/sec; CI, 1.93-2.39).

The change in walking speed during treatment from baseline increased in the fampridine group. The difference in the average percent change from baseline walking speed was higher (p=0.0002) with fampridine (13.6%; CI, 11.4-15.9) compared to placebo (4.7%; CI, 0.7-8.7). The average change in the double-blind walking speed from baseline was higher (p=0.0002) with fampridine (0.28; CI, 0.24-0.33) compared to placebo (0.10; CI, 0.01-0.18). The change from

baseline in walking speed at the end of double-blind treatment was 0.29 (CI, 0.22-0.37) ft/sec for fampridine and 0.10 (-0.03-0.22) ft/sec for placebo (p=0.0072).

Lower extremity strength, tested by LEMMT, increased in the fampridine group. The average change in LEMMT during the treatment from baseline was 0.13 (CI, 0.11-0.16) in the fampridine group compared to 0.04 (CI, 0.00-0.09) in the placebo group (p=0.0016). Baseline LEMMT was not different (p=0.2439) between fampridine (4.06; CI, 3.98-4.15) and placebo (3.97; CI, 3.82-4.11) groups.

Other Endpoints in MS-F204 Trial

Additional Variables in MS-F204 Trial

The sponsor further analyzed two objective and three subjective variables; these were not part of the definitive endpoints. One of the objective variables, average percent change in walking speed, was analyzed *post hoc*. The descriptive summaries of the additional variables are shown in the sponsor's tables below.

Table 15 Additional Objective Variables in ITT Population of MS-F204 Trial (Source: Sponsor's Submission)

	Placebo (N=118)	Fampridine-SR Non-responder (N=68)	Fampridine-SR Responder (N=51)
Baseline Walking Speed in ft/sec: Mean (SD)	2.202 (0.6812)	2.083 (0.7988)	2.162 (0.6892)
Average Percent Change in Walking Speed *			
Mean (SD)	7.67 (18.166)	5.96 (15.523)	24.69 (13.117)
Median	5.16	4.05	22.64
Min, Max	-38.7, 141.1	-42.8, 52.1	5.3, 60.6
Baseline Ashworth Score: Mean (SD)	0.800 (0.6722)	0.884 (0.6045)	0.946 (0.6241)
Average Change in Ashworth Score *			
Mean (SD)	-0.064 (0.3437)	-0.159 (0.3065)	-0.202 (0.3721)
Median	-0.042	-0.125	-0.167
Min, Max	-1.08, 1.04	-0.88, 0.42	-1.08, 0.88

Note: For the Ashworth Score, a negative change is indicative of patient improvement.

*The double-blind average was derived by taking the average of the unmissed visits during Visits 3 through 6.

Table 16 Additional Subjective Variables in ITT Population of MS-F204 Trial (Source: Sponsor's Submission)

	Non-responder (N=175)	Responder (N=62)
n	175	62
Baseline MSWS-12: Mean (SD)	70.03 (21.092)	72.78 (18.649)
Average Change in MSWS-12 Score*		
Mean (SD)	0.85 (10.539)	-6.04 (13.880)
Median	1.04	-3.65
Min, Max	-38.0, 41.1	-55.2, 25.0
Average SGI Score*		
n	175	62
Mean (SD)	4.21 (1.008)	4.76 (0.965)
Median	4.00	4.63
Min, Max	1.0, 7.0	2.0, 6.8

	Non-responder (N=175)	Responder (N=62)
CGI Score at the End of Double-Blind **		
n	162	60
Mean (SD)	3.8 (0.61)	3.4 (0.80)
Median	4.0	3.5
Min, Max	2, 5	1, 5

Note: For the MSWS-12 Score, a negative change is indicative of patient improvement.
For the SGI, a larger value is indicative of a positive patient evaluation
For the CGI Score, a smaller value is indicative of a positive patient evaluation (7 patients did not have a CGI score at the end of the double-blind.

* The double-blind average was derived by taking the average of the unmissed visits during Visits 3 through 6.

**Evaluated at double-blind Visit 6.

Additional Post hoc Analyses for MS-F204Trial

The sponsor reported additional analyses that showed reduction in disability score based on average change in MSWS-12 score in the fampridine responder group compared to non-responders. Similar advantages were reported for the responder group based on the average SGI score and CGI score at the end of double-blind treatment.

The sponsor assessed the potential for treatment unblinding using the summary questionnaires. In the placebo group, 45 % of the subjects felt they received placebo. Similarly, 45% of subjects in the fampridine group felt they received the active drug. In the clinician's assessments, 40-44% of the clinicians were unsure of patient receiving active drug.

Adjustment for Covariates for MS-F204Trial

Adjusting for covariates yielded the same results on reanalyzing the primary and secondary efficacy variables. The sponsor adjusted for the following covariates individually while also adjusting for trial center: gender, weight, height, baseline EDSS score, baseline MSWS-12 score,

and baseline SGI score. The primary efficacy variable (percentage of responders in the treatment groups) showed greater proportion of responders in the fampridine group ($p<0.001$) with each adjustment for covariance. Likewise, the average change in LEMMT by responder group was analyzed adjusting for the following covariates: age, weight, height, duration of disease, baseline EDSS score, baseline MSWS-12 score, and baseline SGI score. Following the adjustments, the fampridine responders had more improvements in the average LEMMT score compared to placebo ($p<0.05$ for each covariate adjustment).

Analyses of Per Protocol Population for MS-F204Trial
The conclusions from the analysis of the per protocol population (N = 197) were supportive of the primary analysis. The responders were 8.2% for placebo and 47.0% for fampridine treatment ($p<0.001$).

Plasma Concentration and Fampridine Response for MS-F204Trial
The sponsor analyzed plasma concentrations of fampridine and its metabolites for fampridine-treated subjects in the MS-F204 trial. The mean plasma concentrations at each visit ranged between 21 and 30 ng/mL during the double-blind period. The maximum concentrations at each visit during the double-blind period were between 56 and 87 ng/mL. The sponsor indicates the results were consistent with earlier PK studies.

Reviewer's Additional Efficacy Results of ITT analysis for MS-F204 Trial
At baseline, average walking speed was not different (p=0.3597) between fampridine (2.12 ft/sec; CI, 1.99-2.25) compared to placebo (2.20 ft/sec; CI, 2.07-2.33)

The average walking speed during the double-blind treatment **was not different** (p=0.7547) between fampridine (2.41 ft/sec; CI, 2.25-2.56) compared to placebo (2.37 ft/sec; CI, 2.22-2.53). Likewise, the walking speed at the end of the double-blind treatment **was not different** (p=0.8029) between fampridine (2.42 ft/sec; CI, 2.26-2.58) compared to placebo (2.39 ft/sec; CI, 2.23-2.55).

However, the average change from baseline in the double-blind walking speed was higher (p=0.0089) with fampridine (0.29; CI, 0.23-0.35) compared to placebo (0.17; CI, 0.11-0.23). Similarly, the difference in the average percent change from baseline walking speed was higher (p=0.0064) with fampridine (14.0%; CI, 10.8-17.2) compared to placebo (7.7%; CI, 4.5%-10.9%). The average percent change from baseline in walking speed at the end of double-blind treatment was 14.8% (CI, 10.7%-19.0%) for fampridine and 8.5% (4.3%-12.7%) for placebo (p=0.0358).

For lower extremity strength tested by LEMMT, there **were no differences** between fampridine and placebo in the following parameters: average LEMMT during double-blind treatment [(4.00; CI, 3.89-4.11) versus (4.00; CI, 3.90-4.11); p=0.9267]; LEMMT at the last observed double-blind visit [(4.01; CI, 3.90-4.12) versus (4.03; CI, 3.92-4.14); p=0.8109]; change in LEMMT at the last observed double-blind visit [(0.10; CI, 0.04-0.16) versus (0.07; CI, 0.01-0.13); p=0.4056]; and average change from baseline in LEMMT [(0.09; CI, 0.05-0.13) versus (0.04; CI,

0.00-0.09); p=0.1246]. Baseline LEMMT was not different (p=0.4784) between fampridine (3.91; CI, 3.80-4.02) and placebo (3.96; CI, 3.86-4.07) treatment groups.

Reviewer's Evaluation of Additional Variables in Pooled Analysis of MS-F203 and MS-F204 Trials

The reviewer evaluated additional variables that were highlighted in the sponsor's pooled analysis. Change from baseline in Ashworth score is shown in table below. During the double blind period, there was no difference between the treatment groups in the Ashworth scores, SGI, and CGI. The lack of between treatment differences in Ashworth scores occurred in spite of a significant change in the score from baseline. Any of the observed changes in Ashworth scores do not appear to change the clinical degree of spasticity. On the average, the subjects remain between no increase in tone and slight increase in tone of muscles. The contribution of such a level of spasticity to walking disability or speed is unclear.

Table 17 Additional Variables in the Pooled ITT population

Variable	Placebo	Fampridine-SR	Total	P value
Ashworth (SE)				
Baseline	0.86 (0.05)	0.89 (0.04)		0.5540
Double blind Average	0.79 (0.05)	0.74 (0.04)		0.4109
Double blind Change from baseline	-0.07 (0.02)	-0.17 (0.02)		0.0012
SGI (SE)				
N	190	343	533	
Baseline	4.47 (0.05)	4.48 (0.07)		0.9787
Double blind Average	4.38 (0.07)	4.51 (0.06)		0.1593
Double blind Change from baseline	-0.10	0.03 (0.07)		0.1201
CGI (SE)				
N	182	323	405	
Double blind End	3.8 (0.06)	3.5 (0.04)		0.0008

The sponsor suggested that an improvement in spasticity may be independent of walking speed improvement. The sponsor's pooled results showed the average reduction in Ashworth Score for the fampridine responders during the double-blind period was 0.15 units compared to 0.07 units for placebo (p = 0.003). The fampridine non-responders also had significantly reduced spasticity of 0.16 units compared to the placebo group (p = 0.009), indicating that improvements in walking speed and spasticity with fampridine may be independent.

6.1.7 Subpopulations

Examination of Subgroups in MS-F203 Trial

All four subtypes of MS recorded an increase in the proportion of responders. The proportions of responders were not different between placebo and fampridine treatment (p=0.309) as shown in the following table:

Table 18 Proportion of Responders by MS Subtype in MS-F203 Trial

Characteristics	Placebo (N = 72)	Fampridine non- responder (N = 160)	Fampridine responder (N = 78)	Total (N = 300)
Relapsing Remitting	21 (29.2%)	47 (31.3%)	15 (19.2%)	83 (27.7%)
Primary Progressive	14 (19.4%)	20 (13.3%)	11 (14.1%)	45 (15.0%)
Secondary Progressive	35 (48.6%)	77 (51.3%)	48 (61.5%)	160 (53.3%)
Progressive Relapsing	2 (2.8%)	6 (4.0%)	4 (5.1%)	12 (4.0%)

Examination of Subgroups for MS-F204 Trial
As in MS-F203 trial, MS-F204 had no formal subgroup analysis. All four subtypes of MS recorded an increase in the proportion of responders. The proportions of Timed Walk Responders among fampridine-treated subjects in the four MS types were: relapsing-remitting 37.2% (16/43); primary progressive 50.0% (5/10); secondary progressive 45.2% (28/62); and progressive-relapsing 40.0% (2/5).

Examination of Subgroups in Pooled Analysis of MS-F203 and MS-F204 Trials
The Timed Walk Responder rates were consistent in the subgroups that the sponsor examined. The subgroups include: gender, race (Caucasians versus non-Caucasians), age, and BMI.

In the sponsor's pooled analysis, the MS subtype, duration of disease, and baseline EDSS did not affect the responder rates. Other baseline characteristics that did not influence the responder rates include: walking speed, LEMMT, Ashworth Score, MSWS-12, and SGI.

The sponsor examined the responder rates in subjects with renal impairment and found no significant change in responder rates. The subjects were categorized as normal (creatinine clearance of 80 mL/minute or above), or abnormal (creatinine clearance below 80 mL/minute). The responder rates were 47.6% in abnormal renal function group compared to 34.7% in normal renal function group (p = 0.825).

With respect to concomitant immunomodulator use, there was a trend to a difference in responder rates between the users and non-users of immunomodulators. The responder rates for placebo-treated subjects were 6.1% for immunomodulator users and 14.9% nonusers, for fampridine-treated were 36.0% for immunomodulator users and 39.8% non-users (p=0.076). The sponsor suggests the trend is likely driven by the high responder rates in placebo-treated nonusers.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Increasing doses of fampridine do not appear to increase efficacy. However, there is a remarkable lack of investigation of doses below 10 mg twice daily.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The efficacy variables returned to baseline values during follow-up visits after the double blind treatments. To address the issue of persistence of efficacy, the sponsor reported interim data from ongoing extension trials (MS-F202 EXT, MS-F203 EXT, and MS-F204 EXT). The extension trials included subjects who participated in the parent double blind trials and received at least one efficacy assessment in the extension trials.

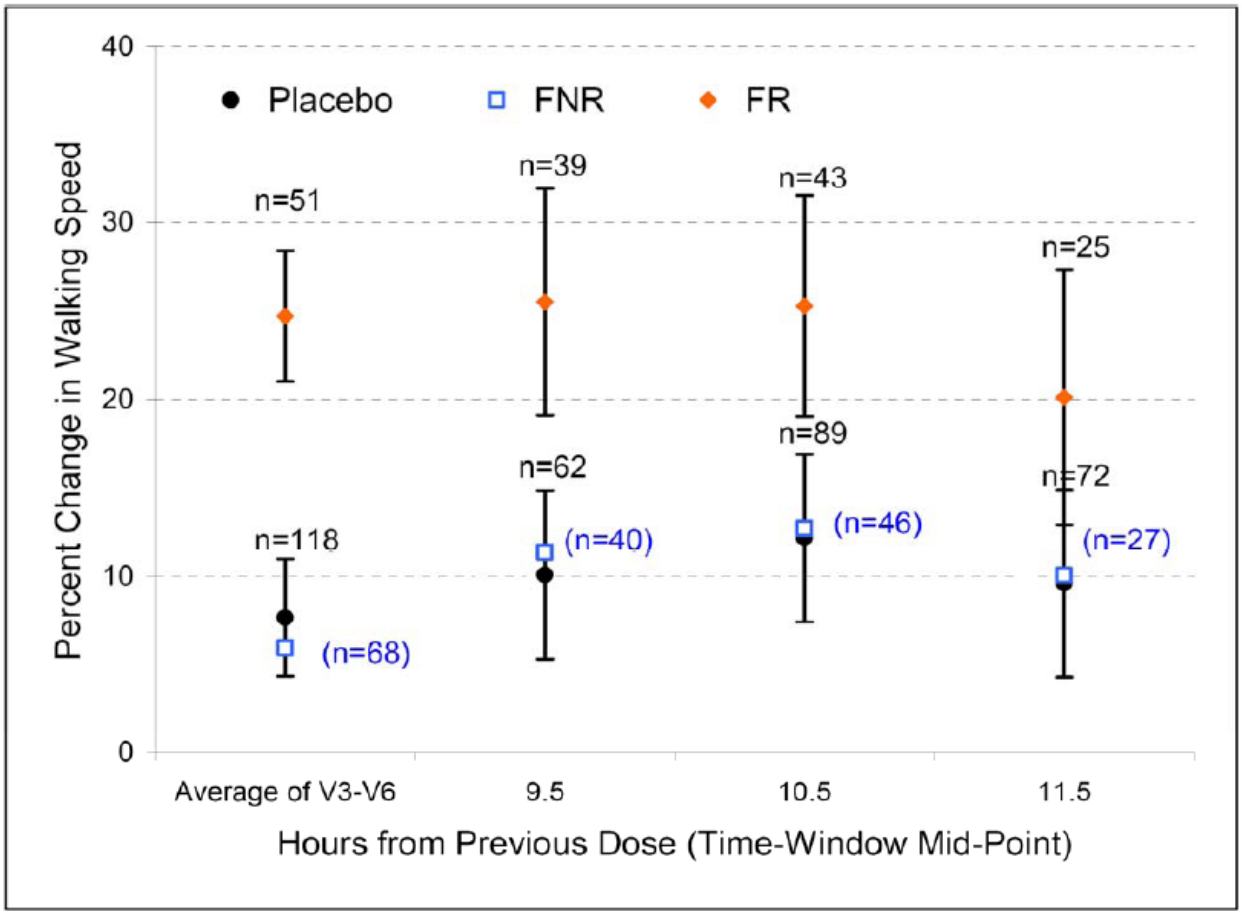
In MS-F203 EXT, the extension Timed Walk Responders were 66 (24.9%). Of these responders, 29 were responders in the parent MS-F203 trial, 25 were nonresponders in the parent MS-F203 trial, and 12 were previously in the placebo group. Among the fampridine double blind responders, the extension responder rates were 42.9% for year 1 and 36.1% for year 2; for fampridine nonresponders, the extension responder rates were 19.7% for year 1 and 17.5% for year 2; and for the placebo patients, the extension responder rates were 16.2% for year 1 and 20.8% for year 2.

The average percent change from baseline in walking speed for the extension timed walk responders was over 30% in year 1, but declined about 10% in year 2 from preceding year level. Similarly, the average percent change in nonresponders improved by 20% in year 1, but declined 8% in year 2 from preceding year level. The sponsor attributed the decline in responder rates in the second year to the natural history of the underlying MS disease.

In MS-F204 EXT, the extension Timed Walk Responders were 105 (49.3%). Among the extension responders, 35 were responders in the parent MS-F204 trial, 18 were nonresponders in the parent MS-F203 trial, and 52 were in the placebo group. The sponsor suggests that these extension responder results indicate absence of tolerance to the treatment effect of fampridine.

Efficacy with Respect to Time from Last Fampridine Dose
The sponsor evaluated efficacy with respect to time from last dose of fampridine in MS-F204. The sponsor evaluated efficacy with respect to time from previous fampridine dose, by conducting a responder analysis, using percent change from baseline in walking speed versus approximate time from previous dose at Visits 3-6 and at the 3 major post-dose time windows at Visit 7. The average walking speed among fampridine responders consistently increased up to 10.5 hours from last dose (Visits 3-6), but declined during the last hour of the 12 hour inter-dosing interval (Visit 7). The changes in average walking speed during the dose interval are shown in figure 4 below adopted from the sponsor's submission.

Figure 4 Walking Speed Change from Baseline at Approximate Times from Previous Dose
(Source: Sponsor's submission; Data from ITT Population, Observed Cases, Mean, 95% CI)



Abbreviations: PBO=Placebo; FNR=Fampridine Timed Walk Non-responders; FR= Fampridine Timed Walk Responders.
Note: Sample sizes for Fampridine 10 mg b.i.d. Timed Walk Non-responders in parentheses, CI not shown for clarity of comparing FNR and PBO.

6.1.10 Additional Efficacy Issues/Analyses

The results of two pivotal trials showed improvements in walking speed in a greater proportion of subjects treated with fampridine compared to placebo. Yet, the magnitude of improvement in the active drug treatment is so small that the walking speed in that group is not significantly different from that of placebo. So, the clinical significance of the treatment benefits is in doubt. One of the major problems of the responder analysis is the inability to predict responders before treatment. If this were possible, a trial in such a population will help determine the real benefits of fampridine treatment. The efficacy of the individual pivotal trials is summarized as follows:

Efficacy Conclusion for MS-F203
The sponsor achieved all three steps of the primary endpoint. More subjects the fampridine group improvement in walking speed measured by the Timed 25-Foot Walk compared to placebo (34.8% vs. 8.3%, p<0.001). The improvement in walking speed, among responders, was maintained through the 14-week double-blind treatment period ($p < 0.001$). Responders in both treatment groups showed improvement in MSWS-12 compared to non-responders ($p < 0.001$). The sponsor presented analyses to support the results of the primary endpoint. The average increase in walking speed over the treatment period compared to baseline was significantly more in the fampridine responder group (25.2%) compared to placebo (4.7%). Leg strength increases occurred with fampridine treatment for both responders ($p < 0.001$) and non-responders ($p=0.046$) compared to placebo.

Efficacy Conclusion for MS-F204
The sponsor achieved the primary endpoint. More subjects in the fampridine group showed improvement in walking speed as measured by the Timed 25-Foot Walk compared to placebo (42.9% vs. 9.3%, p<0.001). The secondary efficacy endpoint, leg strength, increased with fampridine treatment for responders ($p=0.028$) but not for non-responders ($p=0.600$) compared to placebo.

Overall in both pivotal trials, not considering the responder status, fampridine treatment was associated with increased walking speed and increased lower extremity strength from baseline. Despite these increases, there was no difference in walking speed between the fampridine and placebo groups during double-blind treatment.

7 Review of Safety

Safety Summary

A separate review of safety is provided by Dr. Gerard Boehm.

8 Postmarket Experience

None

9 Appendices

None

9.1 Literature Review/References

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9.2 Labeling Recommendations

Label language needs to reflect the drug's improvement in walking speed, in responders, (b) (4) in MS patients. The premise for the sponsor's responder analysis was the ability of the drug to improve walking speed in a subset of patients (responders). The label needs to provide a means of identifying the responders, so non-responders are not unduly exposed to the risk of prolonged drug therapy. (b) (4)

9.3 Advisory Committee Meeting

The reviewer suggested the following questions prior to the advisory committee meeting:
Does the committee believe that the responder status determines a clinically meaningful improvement in walking ability with the small magnitude of change in walking speed observed?

Does the committee believe that the sponsor showed fampridine to improve the walking ability of MS patients to the extent that is clinically meaningful given the potential risk of seizures or other CNS adverse events?

Does the committee believe that additional efficacy trials with smaller doses of fampridine are needed to better define the drug's therapeutic range and safety margin?

Does the committee believe that additional efficacy trials with fampridine dose adjustments are needed to determine appropriate doses for MS patients with mild and moderate renal impairment?

Addendum: The reviewer includes this addendum to provide additional information from the proceedings of the Advisory Committee meeting. The Advisory Committee meeting held on October 14, 2009, with responses to the following questions:

1. Has the sponsor demonstrated substantial evidence of effectiveness of fampridine as a treatment to improve walking in patients with multiple sclerosis (MS)?

Response: The majority (12 of 13 members) voted yes. However, there were divergent views on whether the sponsor demonstrated that this effect was clinically meaningful, either in the group of fampridine-treated patients as a whole, or in a specific subset.

2. Should the sponsor be required to evaluate the effects of doses lower than 10 mg twice daily (BID)?

Response: The majority (12 members) voted yes. However, the majority of the committee also agreed that the evaluation of doses lower than 10 mg twice daily should not be required prior to approval. They agreed that the evaluation was necessary to see if seizure risk and other adverse events are decreased while still maintaining efficacy, thus improving the benefit to risk ratio.

3. Do you conclude that there are conditions under which fampridine SR could be considered safe in use for this indication?

Response: The majority (10 members) voted yes. They agreed that fampridine should not be used in patients with moderate to severe renal insufficiency (baseline serum creatinine or creatinine clearance should be obtained) and in patients with known seizure disorder or are at high risk for seizures. Also, the committee agreed there was no need for pre-screening EEG before initiation of fampridine as no clinical evidence support the use of EEG to predict seizure risk.

This review addresses the following additional issues from the meeting:

1. Proportion of walking speed responders, at different levels of improvement in walking speed, showed additional evidence of superiority of fampridine over placebo.
2. Additional efficacy analyses outside those agreed upon in the SPA may not required.
3. The overall results of fampridine's benefits were supported by the results of the secondary endpoints.

Higher proportions of fampridine patients walked faster at different levels of average percent increase in walking speed from baseline; yet, the level of improvement that is clinically meaningful remains uncertain. The analysis suggested fampridine was superior at different levels between 0% to 60% average increase in walking speed from baseline; at levels between 0% to 40% in average increase in walking speed, the p values were <0.05 comparing fampridine and placebo groups. This analysis has inherent problems. First, the sponsor conducted the analysis on a pooled dataset of three trials (MS-F202, MS-F203, and MS-F204) rather than the two pivotal trials. Second, it was a post-hoc analysis. The sponsor mentioned 20% or more improvement is considered gold standard for clinical meaningfulness. This comment was echoed by advisory committee members. Of note, the 20% benchmark remains to be clearly validated especially with regards to the MS subjects enrolled in the sponsor's pivotal trials. Validation of the 20%

benchmark is from correlating results of timed 25-foot walk (T25FW) with scores on Guy's Neurological Disability Scale (GNDS) or EDSS (Kaufman et al, 2000; and Kragt et al, 2006). These "validating" studies did not evaluate the clinical meaningfulness of >20% improvement in walking speed especially in MS subjects with the degree of walking impairment as enrolled in the sponsor's trials. Rather, the studies suggested >20% increase in the time to walk 25 feet was associated with lower disability scores. Nonetheless, the level of improvement that is clinically meaningful for subjects with the baseline walking speed as those enrolled in the trials remains uncertain.

The Agency required additional efficacy analyses though the pivotal trials conducted under SPAs met the criteria agreed upon. To recognize public health concerns that are not evident at the time of the SPA, the Agency requires a thorough review of the entire NDA submission. Such a review evaluates the drug's efficacy in multiple dimensions. Also, a protocol that a sponsor fails to follow, as stipulated by the SPA, is no longer binding on the review division. Failure to follow SPA specifications reinforces the need to conduct additional efficacy analyses. Such is the case when the sponsor violated the sample size agreements on both SPAs in the fampridine pivotal trials.

The sponsor showed that the fampridine-responders performed better on the secondary outcome variables, yet comparison of the overall treatment groups irrespective of responder status showed no remarkable benefits with fampridine. The Agency analyzed the secondary endpoints by comparing whole treatment groups, rather than by responder status, to maintain the benefits of randomization. In these analyses, there was marginal to no difference between the groups in T25FW, MSWS-12, LEMMT, and SGI at the end of the double-blind period in both trials. These results cast a doubt to the clinical significance of the magnitude of improvement in walking speed with fampridine treatment.

Abbreviations Used

CGI - Clinician Global Impression
CSQ - Clinician Summary Questionnaire
EDSS - Expanded Disability Status Scale
IR - Immediate release
LEMMT - Lower extremity Manual Muscle Testing
MSFC - Multiple Sclerosis Functional Composite Score
MSWS-12 - The 12-Item MS Walking Scale
PD - Pharmacodynamics
PK – Pharmacokinetics
SGI - Subject Global Impression
SR - Sustained release
SSQ - Subject Summary Questionnaire

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KACHIKWU O ILLOH
12/11/2009

ERIC P BASTINGS
12/24/2009
Please refer to my CDTL memo for a discussion of differences of opinion with some of Dr. Kachi's conclusions and recommendations.

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA:	22-250
Drug:	Fampridine SR (Amaya)
Route:	Oral
Indication:	To improve walking ability in patients with multiple sclerosis (MS)
Sponsor:	Acorda
Submission Date:	1/30/2009; resubmitted on 4/22/09
Review Date:	11/30/09
Reviewer:	Sally Usdin Yasuda, Safety Team Leader Neurology Drug Products, HFD-120

1. Background

Fampridine (2-aminopyridine) has been proposed to improve walking ability in patients with multiple sclerosis (MS). The mechanism of action of fampridine is thought to be due to blockade of potassium channels resulting in restoration of action potential conduction in demyelinated nerve fibers.

Clinical studies have been conducted to evaluate the use of fampridine in various indications including MS, spinal cord injury (SCI), and Guillain-Barre Syndrome. The adverse event of greatest concern in the development program has been seizures that appear to be related to dose and to Cmax. For this reason, the controlled release formulation of fampridine (fampridine SR) was developed and has been used in the well-controlled and adequate studies that have been submitted to support this NDA. In addition, the Sponsor proposes a dose of fampridine SR 10 mg bid to minimize the risk of seizures.

This memorandum primarily summarizes the findings of Dr. Jerry Boehm's primary safety review of the fampridine SR NDA for MS. Please refer to Dr. Boehm's review for more detail. Drs. Kachi Illoh and Billy Dunn have also considered the narratives for the reports of the seizures, and Dr. Jody Green has commented on the data regarding MS relapse. Their comments have been taken into consideration in Dr. Boehm's review as well as in my review.

2. Summary of Findings from the Safety Review

2.1 Sources of Data

The clinical data evaluated in the safety review are from studies submitted as part of the NDA, and include studies in MS subjects (clinical pharmacology, controlled, and uncontrolled trials), spinal cord injury (SCI) subjects (clinical pharmacology, controlled, and uncontrolled trials), and non-patient subjects (healthy volunteers, volunteers with renal impairment). There were 45 trials that contributed to the pooled safety database and there was also safety data from 11 trials that were not pooled due to lack of available data sets from the previous

IND holders. A thorough QT study was conducted and submitted to the IND. Dr. Boehm's review relies primarily on the analyses of the pooled safety population for MS subjects and SCI subjects for overall risk estimates. For comparative risk analyses, his review relies primarily on data from the adequate and well-controlled MS trials (MS-F202, FS-F203, and MS-F204).

Characteristics of the adequate and well-controlled studies in MS are summarized below, as taken from Table 1 in the ISS.

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race[1]
MS-F202 24 MS Patients (Adequate/well-controlled study)	Double-blind, placebo-controlled, 20-week, parallel group 27-Feb-03 18-Dec-03	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR Placebo Oral doses administered b.i.d. for 15 weeks	206	75 (36%), 131 (64%) 49.8 yrs. (28, 69) 92.2% Caucasian 4.9% Black 1.5% Hispanic 1% Other 0.5% Asian/Pacific Islander
MS-F203 33 MS Patients (Adequate/well-controlled study)	Double-blind, randomized, placebo-controlled 07-Jun-05 28-Jun-06	10 mg FAM-SR Placebo Oral doses administered b.i.d. for 14 weeks	300	95 (32%), 205 (68%) 51.4 yrs. (26, 70) 92.9% Caucasian 7.1% Non-Caucasian
MS-F204 35 MS Patients (Adequate/well-controlled study)	Double-blind, randomized, placebo-controlled 22-May-07 27-Feb-08	10 mg FAM-SR Placebo Oral doses administered b.i.d. for 9 weeks	239	77 (32%), 162 (68%) 51.7 yrs. (24, 73) 91.2% Caucasian, 5.0% African-American, 1.7% Hispanic, 1.7% Other, 04% American Indian/Alaskan Native

According to Dr. Boehm's review, the NDA includes 1922 subjects exposed to one or more doses of fampridine (1621 exposed to fampridine SR). These included 1793 subjects in the integrated safety database and 129 from the excluded trials. There were 917 MS subjects exposed to fampridine (807 exposed to the SR formulation). There were 792 subjects in the integrated database exposed to all fampridine formulations for ≥6 months (601 MS subjects exposed and all of those MS subjects exposed to fampridine SR). There were 456 subjects in the integrated database exposed to all fampridine formulations for ≥ 1 year (including 405 MS patients, all of whom were exposed to fampridine SR, and over 300 of whom were exposed to fampridine 10 mg bid). The database fulfills minimum ICH requirements for evaluation of a new drug (at least 1500 subjects; 300 subjects for 6 months and 100 subjects for 1 year at the doses proposed for marketing).

2.3 Significant Safety Findings

2.3.1 Deaths

Dr. Boehm notes that there were 6 deaths in the fampridine development program included in the integrated safety database that occurred within 30 days of last exposure to fampridine SR (5 in MS subjects and 1 in a SCI trial subject). One additional death in a MS trial subject occurred 5 weeks after the last fampridine SR exposure. There was also 1 death in a placebo subject in a SCI trial. There were no deaths reported from the fampridine trials excluded from the integrated safety analysis.

The 5 deaths that occurred within 30 days of last exposure in the MS subjects all occurred during open label extension phases of the trials. Four subjects were taking 10 mg bid fampridine SR and one was taking 15 mg bid. The four subjects taking 10 mg bid were taking fampridine at the time of death; the fifth subject had been off fampridine for 14 days at the time of her death. The reported causes of death were oxycodone overdose[1], aortic dissection (in a patient with a history of elevated cholesterol and with screening blood pressure of 150/96 and on-treatment blood pressure of 130/94), suicide, unknown/found dead in bead, intracranial hemorrhage (due to aneurysm in a patient with a history of hypertension), and fall (positional asphyxia, SCI patient taking 40 mg bid prior to death). The cause of death in the MS subject that occurred 5 weeks after last exposure was documented by autopsy as ischemic and hypertensive heart disease in a patient with a history of risk factors. There was an additional death due to intracranial hemorrhage in a patient taking fampridine for over 4 years in an ongoing MS trial reported in the Safety Update. Please refer to Dr. Boehm's review for details of these deaths.

There does not appear to be a pattern suggesting that the deaths were drug-related.

2.3.2 Other Serious Adverse Events

Overview of SAES in the pooled safety population– Dr. Boehm notes that 15.1% (228 /1510) of fampridine SR MS and SCI subjects experienced one or more SAEs. The System Organ Class (SOC) groupings with the most SAEs were Nervous system disorders (5.4%) and Infections and Infestations (4.3%). No other SOC grouping included > 1% of subjects. Dr. Boehm has provided a list of SAEs reported by at least 3 fampridine subjects in the pooled MS and SCI trials. The most frequent were MS relapse (n= 38, 2.5%), convulsion (n=19, 1.3%), urinary tract infection (n=18, 1.2%), and cellulitis (n=16, 1.1%). There was 1 SAE of pancytopenia and 1 SAE of pancreatitis, both described below.

No subjects experienced SAEs of hepatic failure, hepatitis, rash, Stevens Johnson syndrome, Toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, or aplastic anemia.

[1] Fampridine would not be expected to interfere with the metabolism of oxycodone as fampridine does not appear to be an inhibitor of CYP2D6.

Dr. Boehm has reviewed the following select SAEs of interest in the pooled safety population and I summarize those below:

Encephalopathy - Three subjects had SAEs of encephalopathy. In subject ACD-001235 this occurred 15 days after stopping fampridine (for seizure) and the event was attributed to baclofen. The event in subject ACD-000202 who mistakenly took up to 300 mg baclofen and then suddenly stopped was attributed to baclofen withdrawal; the subject continued to take fampridine. Subject ACD-001246 received fampridine for approximately 1 month, titrated to 30 mg bid, and experienced encephalopathy with associated hypokalemia and possible seizure. She had abruptly withdrawn from chronic use of clonazepam and Prozac on the day of the event and was in a confused state. She was treated with lorazepam and potassium replacement, after which she made a full recovery. These events cannot be clearly attributed to fampridine.

Anemia - Three subjects had SAEs of anemia, one presumed due to upper GI bleed in a subject with frequent NSAID use treated with steroids, one attributed to ulcerative colitis, and one attributed to anemia of chronic disease.

Pancytopenia – Subject ACD-000628 was a 45 y.o. male with SCI who had taken fampridine for 2 months at the time of the event. Labs are shown below. Fampridine was stopped after the last visit and the subject was reported as having pancytopenia. The subject reported experiencing a GI illness with diarrhea just prior to this event. Repeat labs were performed 7 days later.

	WBC (nl 3.5-10.5 k/mm^3	Hgb (nl 13-17.5 g/dL)	Platelet (nl 140-370 $k/mm^{3)}$
Baseline	7.48 k/mm^3	14.4 g/dL	202 k/mm^3
Last visit (after 2 months of fampridine)	3.45 k/mm^3	12.8 g/dL	193 k/mm^3
Repeat labs	6.18 k/mm^3	14 g/dL	245 k/mm^3

Pancreatitis - Subject ACD-000451 was a 47 y.o. male who taking no other medications at the time he was diagnosed with pancreatitis secondary to cholelithiasis. He underwent laproscopic cholecystectomy. The event resolved and he discontinued from the trial.

SAEs in MS subjects, controlled and uncontrolled trials – 19.3% (177 of 917) of fampridine SR MS trial subjects experienced one or more SAEs. These were similar to those in the pooled population and included MS relapse (4.1%, n=38) and convulsion (1.4%, n=13) that were the most frequent. Three MS subjects experienced SAEs of complex partial seizures (0.3%).

SAEs in adequate and well controlled MS trials – SAEs were 3 times more frequent among fampridine SR subjects (6.5%, 33/507) compared to placebo subjects (2.1%, 5/238) and the risk for all SAEs among fampridine SR subjects

appeared dose related. MS relapse was the only SAE that occurred in more than 2 fampridine SR subjects (fampridine n=7, 1.4%; placebo n=0).

SAEs in SCI subjects, controlled and uncontrolled trials – In SCI trials, 8.6% (51/593) subjects experienced one or more SAEs and these were similar to those reported in the pooled population.

SAEs in non-patient population – One patient (0.3%, 1/382) in this population reported an SAE (visual hallucinations).

SAEs in non-pooled trials –Following 5 doses of 4-aminopyridine (12.5 mg q 6 hours), a female MS patient from a clinical pharmacology trial (1091-001US) experienced what was described as a tonic-clonic seizure lasting 30 seconds with loss of consciousness lasting 1 minute. Plasma levels in the hospital at an unknown interval following the event were 104ng/mL. In a Guillain-Barre trial, a 77 y.o. male experienced 2 days of tachycardia after 3 weeks of 4-aminopyridine treatment. Tachycardia resolved without treatment. Treatment with 4-aminopyridine continued throughout the event; the subject completed the trial.

SAEs in the safety update – Seventeen fampridine SR patients experienced 28 SAEs during the period covered by the Safety Update. These included 3 MS relapse, 2 syncope, and 1 each of intracranial hemorrhage, pyrexia, dehydration, renal mass, urinary tract infection, pulmonary embolism, fall, appendicitis perforated, post-operative wound infection, adenocarcinoma, depressed level of consciousness, septic shock, Escherichia infection, pancreatitis, cholelithiasis, peripheral vascular disorder, chest discomfort, myocardial infarction, abdominal pain upper, nausea, vomiting, bile duct stenosis, and suicide attempt. No new seizure SAEs were reported.

2.3.3 Dropouts

In the *pooled MS and SCI trials*, 14.6% (221/1510) fampridine SR subjects experienced one or more (TE) adverse events (AEs) leading to discontinuation. The SOC groupings with the most TEAEs leading to discontinuation were Nervous system disorders (8.5%), psychiatric disorders (4.2%), general disorders and administration site conditions (3.4%), Gastrointestinal disorders (2.5%), and Musculoskeletal and connective tissue disorders (1.89%). The most common preferred terms (> 1%) were dizziness (2.5%), insomnia (1.5%), convulsion (1.3%), asthenia (1.3%), nausea (1.1%), and anxiety (1.1%). The following TEAEs led to discontinuation of 1 subject each: pancreatitis (described as SAE above), hypersensitivity (noted as rib pain and “increased hypersensitivity”), rash macular (developed after approximately 13 months of fampridine SR and persisted despite treatment with topical hydrocortisone for 3 months), skin exfoliation/toxic skin eruption on hands and trunk with peeling skin on hands (treated with corticosteroids and resolved within approximately 1 week). No subjects discontinued for hepatic failure, hepatitis, Stevens Johnson syndrome,

toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, pancytopenia, or aplastic anemia.

TEAEs leading to discontinuation of MS trial subjects, controlled and uncontrolled trials – Eleven percent (102/917) of MS subjects in this group had one or more TEAEs leading to discontinuation. The most common were convulsion (1.4%, n=13), balance disorder (0.9%, n=8), dizziness (0.8%, n=7), and asthenia (0.7%, n=6). Three MS subjects discontinued for TEAEs of complex partial seizures.

TEAEs leading to discontinuation from adequate and well-controlled MS trials - Overall, 3.4% (17/507) of fampridine SR subjects had TEAEs that led to discontinuation compared to 2.1% (5/238) on placebo. Those that occurred in at least 2 fampridine subjects and more frequently than placebo were headache (fampridine 0.8%, placebo 0), balance disorder (fampridine 0.6%, placebo 0), dizziness (fampridine 0.6%, placebo 0), and confusional state (fampridine 0.4%, placebo 0). One fampridine SR and no placebo subjects discontinued for convulsion and no subjects discontinued for complex partial seizures.

TEAEs leading to discontinuation for the non-patient population – Four fampridine SR subjects (1%) had one or more TEAEs that led to discontinuation from this group. Those that occurred in at least 3 subjects were dizziness and tremor, both occurring in 3 subjects.

AEs leading to discontinuation in the non-pooled trials – Four subjects experienced AEs leading to discontinuation in this group and all were Guillain-Barre patients. Discontinuations were for a “chronic demyelinating polyneuropathy”; tremor, cramping, weakness, dizziness, ataxia, and diabetic hypoglycemia; weakness tremors, postural hypotension; and dizziness.

TEAEs leading to discontinuation in the safety update – 4 Fampridine SR subjects discontinued in this group. The events leading to discontinuation were myocardial infarction, depressed level of consciousness, intracranial hemorrhage (also reported as a death, above), and trigeminal neuralgia.

2.3.4 Significant Adverse Events

Seizure risk was an event of special interested identified prior to the submission of the NDA. Dr. Boehm has evaluated seizure risk, risk of MS relapse, psychiatric AEs, urinary tract infection, and hepatic injury as significant AEs. I will summarize his findings here. Please refer to his review for a more detailed discussion.

Seizures – The discussion of seizure risk considers the results of nonclinical studies as well as clinical data. The clinical data includes MS subjects exposed to the proposed fampridine SR dose (10 mg bid), as well as risk in MS subjects exposed to higher fampridine SR doses, MS subjects exposed to other fampridine formulations, and in SCI subjects (most of whom were exposed to

doses > 10 mg bid). There were no seizures reported to be observed in MS subjects in clinical pharmacology trials.

Nonclinical *in vitro* studies showed amygdala and hippocampus epileptiform discharges when perfused with solutions of fampridine at concentrations of 5 to 500 uM. Nonclinical studies in rats and in dogs exposed to fampridine found seizures that appeared to be dose related, and related to Cmax.

The Sponsor cited an estimate of seizure prevalence in the general population of 0.5-1.0%, and an annual epilepsy incidence in the general population of 50/100,000. Dr. Boehm has reviewed available information regarding seizure risk in MS patients. One author has reported a range of seizure prevalence estimates in MS patients between 2-4%, although Dr. Boehm points out that many of the over 30 publications from which these estimates are derived did not distinguish between seizures that predated MS and those that arose after symptoms or diagnosis of MS. In four publications that reported epilepsy or seizure incidence or included incident cases of seizure and person time follow-up data, epilepsy incidence in MS patients have been reported to be 140/100,000 PY (Olafsson et al), age adjusted mean annual incidence of 148/100,000 (Nicoletti et al), yearly incidence of first seizure without identified cause of 349/100,000 (Eriksson), and incidence of seizure without identified cause after diagnosis or after development of symptoms but prior to diagnosis of 61/100,000 PY and 80/100,000 PY, respectively (in that case the study's general population background was 61/100,000 PY; Nyquist et al).

In order to minimize the risk of seizures in the fampridine clinical trials in MS, Acorda excluded patients with a history of seizure, and screened patients with EEGs prior to enrollment in MS randomized controlled trials and again after completing a randomized controlled trial and prior to entering an open label extension. Subjects were excluded if they had "evidence of epileptiform activity" (not defined) on screening EEG. In the adequate and well controlled studies in MS and in MS-F201, up to 4.1% of screened subjects were excluded for EEG abnormalities, and a total of 36/1076 subjects screened for these 4 studies (3.3%) were excluded. In addition, 11/885 (1.2%) of subjects screened for the MS extension trials were excluded for EEG abnormalities.

In the randomized, placebo controlled MS trials (MS-F201, MS-F202, MS-F203, and MS-F204) 532 subjects were randomized to fampridine and 249 to placebo. Five seizure AEs (0.9%) were observed in fampridine subjects and 1 (0.4%) in a placebo subject in pooled results of the 4 trials. Dr. Boehm considers the results of MS-F201 separately as it included fewer subjects and titrated to higher doses.

IN MS-F201, 25 subjects were randomized to fampridine and 11 to placebo. Fampridine subjects started at 10 mg bid and dose was increased in weekly intervals to a target dose of 40 mg bid. No placebo and 2 fampridine subjects

(8%) experienced seizures. The fampridine subjects were receiving 30 mg bid and 35 mg bid at the time of the seizures, and are described below.

> Subject 03002, a 55 y.o. female, experienced an episode of encephalopathy and a possible tonic seizure, observed by paramedics. The narrative reported "tremulousness" without rhythmic jerking; EEG found no focal or epileptiform activity. Three days before the event after a week of 25 mg bid treatment, plasma fampridine concentration was 117.0 ng/ml. Although a contribution of fampridine cannot be ruled out, the case was complicated by the fact that the patient had suddenly stopped taking clonazepam and began a new treatment with sumatriptan for migraine just prior to the event. Other medications included Prozac and Excedrin. The patient was experiencing hypokalemia and refractory migraine at the time. Seizures are noted in the labeling for both sumatriptan and Prozac and the labeling for clonazepam discusses withdrawal symptoms (including convulsions) and cautions against abrupt discontinuation.
>
> Subject 02006, a 61 y.o. female, experienced a period of confusion, apnea, and possible seizure at a dose of 35 mg bid and was hospitalized for 2 days. In the previous weeks of treatment, fampridine concentrations had been 44.4 ng/ml at 15 mg bid, 61.6 ng/ml at 20 mg bid, and 99.6 ng/ml at 25 mg bid. Three days prior to the event, and following a week of treatment at 30 mg bid, the plasma concentration was below the limit of quantitation (< 2 ng/ml). The same patient experienced an episode of encephalopathy and possible seizure considered secondary to baclofen treatment (b) (6) days after discontinuation of fampridine-SR. Other concomitant medications included estrogen, progesterone, amitriptyline, fosamax, and Fleets suppository. Although this case is confounded, if seizures are related to Cmax it is possible that rapid exposure to concentrations achieved with 30 mg bid (without titration from undetectable concentrations that would indicate noncompliance) could be associated with seizures in the first event. It does not seem likely that the second episode is related to fampridine as even in the worst case of severe renal impairment the half-life of the drug is an average of 14.3 hours (compared to 5-6 hours in normal renal function) and it is unlikely that drug was still present at the time of the event.

Dr. Boehm has summarized the seizure risk data for the 3 adequate and well controlled MS trials as follows (note that Acorda included all subjects exposed to the 10 mg bid dose group in the denominator for that dose group, n=532; Dr. Boehm has included only those subjects randomized to that dose group since subjects titrated to higher doses received this dose briefly during titration; I agree with Dr. Boehm's more conservative approach):

Seizure Risk Data for MS Trials MS-F202, MS-F203, and MS-F204

Study	Placebo	Total	Fampridine	Fampridine	Fampridine

		Fampridine	10mg BID	15mg BID	20mg BID
MS-F202	(0/47)	1.3% (2/159)	(0/52)	(0/50)	3.5% (2/57)
MS-F203	(0/72)	0.4% (1/228)	0.4% (1/228)	-	-
MS-F204	0.8% (1/119)	(0/120)	(0/120)	-	-
Total	0.4% (1/238)	0.6% (3/507)	0.3% (1/400)	(0/50)	3.5% (2/57)
	1.6/100 PY (1/62PY)	2.1/100 PY (3/142PY)	0.9/100 PY (1/108PY)	- (0/16 PY)	11.8/100 PY (2/17PY)

I agree with Dr. Boehm's conclusion that the pooled data demonstrate an increased seizure risk between all fampridine SR subjects and placebo subjects and that, based on a small number of events and limited exposure, it appears the there is an increased risk at 20 mg bid.

Dr. Boehm has provided details of the seizure events for which there was information submitted. These have also been reviewed by Drs. Dunn and Illoh who agreed that the events in the fampridine SR subjects were likely seizures. I will summarize the cases as well as several of Dr. Illoh's comments that were communicated in an email of 7/17/09.

> Subject 14003 from MS-F203 was a 58 y.o. female assigned to 10 mg bid fampridine SR. After (b) (6) days on double blind treatment she experienced sepsis secondary to community acquired pneumonia. In the ER she experienced an apparent focal seizure involving shaking of an extremity. It is not known when she took her last dose of fampridine SR prior to the event. Concomitant medications at the time of the event included oxybutynin, Prozac, oxycodone, calcium, fosamax, avonex, Tylenol, and Bactrim DS. The role of fampridine in this case is unknown.
>
> Subject 04006 from MS-F202 was a 58 y.o. male taking fampridine SR for (b) (6) days when he experienced a generalized seizure, approximately 7.5 hours after his last dose of 20 mg fampridine SR (to which he had been titrated 5 days earlier). He had tongue lacerations. A CT scan was unremarkable. He was treated with methylprednisolone, fosphenytoin, and Dilantin and was discharged the following day. Five days earlier, his plasma fampridine concentration at approximately 6 hours post-dose was 35.5 ng/ml. Concomitant medications at the time of the event were baclofen and Viagra. The role of fampridine cannot be ruled out.
>
> Subject 07019 from MS-F202 was a 47 y.o. woman who experienced a partial complex seizure after taking a double dose of 20 mg fampridine SR (total 40 mg) to compensate for a previously missed dose. On the day of

the overdose (at a scheduled visit after (b)(6) days on double blind treatment) the plasma fampridine concentration at approximately 4.5 hours post dose was 79 ng/ml. She experienced a partial complex seizure of moderate severity 4 hours later. The patient was allowed to continue in the trial, but (b)(6) days later she again took 2 doses within a short period of time. She became confused for about an hour and was discontinued form the study at that point. Dr. Illoh agreed with seizures (partial complex) for both events. Concomitant medications included betaseron and Lexapro (escitalopram), confounding the case. However, in the setting of the high dose of fampridine and the time course of the events, the contribution of fampridine is quite plausible.

Subject 028/408 from MS-F204 was a 65 y.o. female who experienced an AE coded as complex partial seizures after (b)(6) days on placebo. She had "watched an entire move, and upon completion was not able to recall the title or details of the movie". The investigator felt that the patient possibly had a complex partial seizure. On the subsequent 2 days the patient lost her balance and fell, with no significant injuries noted, but other symptoms noted around this time included increased fatigue, difficulty with short-term memory, and worsening gait imbalance. An EEG (b)(days after the event showed no evidence of epileptiform activity but did show mild intermittent bitemporal slowing, more prominent on the left side, and her screening EEG showed mild intermittent left temporal slowing. Dr. Boehm reports that Drs. Dunn and Illoh disagreed about whether the event reported for the placebo subject represented a seizure.

Dr. Boehm has summarized the seizure risk and events in the open label MS trials. He has provided Table 13 from the ISS as shown below.

Seizure Incidence and Dose at Time of Occurrence in Open-Label Extension Trials of Fampridine SR in MS through July 31, 2008 (from Dr. Boehm's review)

	MS-F202EXT >10mgbid*	MS-F202EXT 10mgbid	MS-F203EXT 10mgbid	MS-F204EXT 10mgbid	Total 10mgbid
Subjects exposed	175	177	269	214	660
Patient years	115	422	513	125	1060
Subjects with seizure AE	2	1	4 [1,2]	0	5
%	1.14%	0.56%	1.5%	0	0.76%
Incidence per 100 PY (95% CI)	1.7 (0.21-6.28)	0.24 (0.01-1.32)	0.78 (0.21-2.00)	0	0.47 (0.15-1.10)

*Using the exposure datasets, Dr. Boehm determined that the person time exposure in 202EXT at >10mg bid is almost entirely to 15mg bid, with <2PY exposure to 20mg bid.

[1] One of these cases was a patient taking a very high dose of Detrol-LA (tolterodine) 12 mg b.i.d. at the time of the seizure. She discontinued from both fampridine and Detrol and experienced another seizure one year later, on resuming Detrol treatment.
[2] One additional patient (#23015) experienced seizure at 22 days following discontinuation from Study MS-F203EXT due to an MS relapse. This patient was not included here as the event, given the length of time off treatment, the rapid clearance of fampridine, and the lack of any known association between withdrawal and seizure. The event was evaluated by the investigator as unlikely related to treatment.
bid = Twice daily; CI = Confidence interval; EXT = Extension; MS = Multiple sclerosis; SR = Sustained release.

The cases are described as follows:

Subject 25016 was a 60 y.o. female who received fampridine in a preceding controlled trial and started open label fampridine 10 mg bid in study F203-EXT on (b) (6). On (b) (6) she started tolterodine (8 mg followed by 12 mg taken 12 hours later) and on (b) (6) she was observed with body rigid and convulsing for approximately 3 minutes, occurring approximately 9 hours after the last dose of fampridine ER. Fampridine and tolterodine were stopped. She restarted tolterodine in (b) (6) and on (b) (6) experienced a grand mal seizure. Concomitant medications included Aricept and Diovan. Of note, the initial recommended dose of tolterodine is 2 mg twice daily. I have found a mention of seizures with tolterodine overdose at http://www.medicinenet.com/tolterodine-oral/page2.htmI , but not in the approved label of the drug. I agree with Dr. Illoh's comments in his email of 7/17/09 that although the dose of tolterodine was high, and if tolterodine is associated with seizures in overdose, the role of fampridine or the combination of the two drugs in the first event cannot be ruled out.

Subject 16001 was a 46 y.o. female who received fampridine in a preceding controlled trial and started open label Fampridine SR 10 mg bid on (b) (6) Concomitant medications included betaseron and baclofen. On (b) (6) she was found in the bathroom shaking and had vomited. She had a prolonged period of several hours of seizures despite treatment with phenytoin and Ativan, and later phenobarbital. The role of fampridine in this event is unknown.

Subject 35002 was a 64 y.o. male who received fampridine in a preceding controlled trial and started open label fampridine SR 10 mg bid on (b) (6) on (b) (6) he reported visual disturbances and noted that he was leaning to one side. When his wife arrived she witnessed him shaking and unconscious. An EEG report on (b) (6) noted "…excessive fast activity which may be related to medication effect…". Because of additional findings on the EEG, a sleep deprived EEG was performed and was reportedly normal. The subject discontinued from the trial. The role of fampridine, given at the propose dose, in this case is unknown.

Subject 21009 was a 62 y.o. female who received fampridine in a preceding controlled trial and started on open label fampridine SR 10 mg bid on (b) (6) On (b) (6) while at a rehabilitation facility recovering from a fall, a physician witnessed a 90 second episode of generalized rigidity and rhythmic shaking during and after which she was unresponsive for 10-15 minutes. Dr. Illoh notes that the event of fall may have been from a seizure rather than MS exacerbation, given lethargy and amnesia associated with the event. EEG was not done or the results were not stated for this event. Dr. Illoh agrees with seizures for the event on 5/2 and notes that this was on the proposed dose of fampridine SR.

Subject 22031,a 48 y.o. female, received fampridine in a controlled trial and then started treatment with open label fampridine SR 10 mg bid on (b) (6). She was titrated to 15 mg bid on 7/14/04 and remained on that dose until (b) (6) when she was titrated down to 10 mg bid. On (b) (6) she experienced an event diagnosed as partial complex seizure. She also reported an episode of "shaking of the trunk". She did not report these events until 8/16/07. She also reported 2 episodes of undiagnosed "convulsions" during sleep that occurred 1 and 2 years prior to the event. She was taking no other medications at the time of the event.

Subject 22024 was a 59 y.o. female who received placebo in a preceding controlled trial and started open label fampridine SR 10 mg bid on 6/8/04. She was titrated up to a dose of 15 mg bid on (b) (6). On (b) (6) she experienced a seizure that was not described. EEG showed mild, diffuse encephalopathy with epileptic activity in the left hemisphere suggesting the possibility of a recent CVA; epileptiform abnormalities were not evident approximately 6 weeks after the event. She was treated with Dilantin and switched to Keppra and was discontinued from the trial. Concomitant medications were Reminyl, azathioprine, and baclofen.

Subject 22039 was a 63 y.o. male who received placebo in a preceding controlled trial and started open label fampridine SR 10 mg bid on 8/5/04. He was titrated to 15 mg bid on (b) (6). On (b) (6) he experienced a generalized motor seizure. He reported symptoms of gastroenteritis for a few days prior to the event. An EEG found mild to moderate diffuse encephalopathy. He was treated with carbamazepine and was discontinued form the study. Concomitant medications were lovastatin and baclofen.

Six of 178 (3.3%) MS subjects exposed to other fampridine formulations experienced seizure AEs, all classified as generalized seizures. Three cases with onset within 3 days occurred after doses of 40 mg bid, 12.5 mg q 6h, and 2 doses of 12.5 mg given 7 hours apart and an accidental overdose of 25 mg after another 9 hours. Plasma samples from these patients showed concentrations of > 100 ng/ml. One event occurred after treatment for 22 months at a dose of 12.5

mg bid. One occurred after 8 days of treatment with 12.5 mg bid, and the final case occurred after 26 days of treatment at a dose of 17.5 mg bid.

In the double blind controlled SCI trials, one fampridine (0.27%, 1/372) and no placebo subjects (0/324) experienced a seizure. The seizure occurred in a subject exposed to 40 mg bid (4.3%, 1/23). No seizures were reported in subjects exposed to 17.5 mg bid, 20 mg bid, or 25 mg bid. In open label SCI trials, 5 SCI subjects (1.4%, 5/354) experienced seizures. On subject was taking 25 mg bid and the remaining four were taking 30 mg bid, 35 mg bid, and 40 mg bid (n=2). Baclofen was a concomitant medication in each of these events, and Zanaflex in two of them.

Dr. Boehm reports that Acorda believes the data support that concentrations of 100 ng/ml are like to represent a threshold for increased risk of seizure in absence of other significant risk factors, although the Sponsor conceded that seizures have occurred in patients where plasma concentrations were likely in the normal therapeutic range.

Dr. Boehm presents a summary of seizure risk form Rebif and Avonex and notes that both have information in the precautions sections regarding cautions when administering these medications to patients with pre-existing seizure disorders. Copaxone and Betaseron also have seizures mentioned in the labels, although not in the precautions.

I agree with Dr. Boehm's conclusion that fampridine is associated with seizure risk, and that the relevant question is whether there is an increased seizure risk at the dose intended for treatment of MS patients (10 mg bid). Dr. Boehm notes that although the data from the controlled trials at this dose did not suggest a seizure risk compared to placebo, this relies on a small number of fampridine treated patients and only 2 events. I have the following specific comments about fampridine and seizure risk:

- With a doubling of the dose in the controlled trials (from 10 mg bid to 20 mg bid), the seizure risk was 10-fold higher.
- The dose-concentration relationship shows overlap in Cmax between the 10 and 15 mg doses, according to clinical pharmacology data presented by Dr. Boehm at the advisory committee.
- Without dosage adjustment in patients with severe renal impairment, similar concentrations might be expected, as a doubling of the concentration was observed. There is no dose available that would allow for dosing in these patients. Even in patients with mild-moderate renal impairment a 60% increase in plasma concentrations is observed as a result of a decrease in fampridine clearance by 42.7% in patients with mild renal impairment (CLcr ≥50–80 mL/min) and by 50.3% in patients with moderate renal impairment (CLcr = 30–50 mL/min). As seen with the Cockcroft Gault formula for creatinine clearance, below, even patients with seemingly normal serum creatinine levels could have estimated creatinine

clearance in the mild impairment range, depending on age. (A 60 y.o. male weighing 70 kg with a serum Cr of 1.0 would have an estimated CrCl of 78 ml/min; a 55 y.o. female weighing 70 kg with a serum Cr of 1.0 would have an estimated CrCl of 70 ml/min). Therefore, it will be important for physicians to take this into consideration.

Cockcroft Gault formula for creatinine clearance:

$$CrCl = \frac{(140 - age) \times weight(kg)}{SerumCr(mg/dl) \times 72}$$

Multiply by 0.85 for women.

- Dr. Boehm also notes that this was a highly selected group of patients who were screened by history and by EEG. Dr. Boehm recommends that if fampridine is approved, it should not be used in patients with seizure history and prospective patients should be screened with EEG prior to treatment, the conditions of use in the clinical trials. Alternatively, the labeling could describe the conditions of use in the clinical trials, and a Risk Evaluation and Mitigation Strategy (REMS) could include a program to better characterize the risk. The labeling should fully explain the risks, and a medication guide should explain the risk to patients.
- I would also suggest that some consideration be given to the potential risk of giving concomitant medications that can lower the seizure threshold.
- Finally, I am concerned about rapid titration to high doses, such as in the setting of taking an extra dose following a missed dose. I agree with the Sponsor's labeling proposal that says, "patients should not take double or extra doses if a dose is missed".

MS Relapse – As Dr. Boehm notes, results form the pooled analysis of AEs from the adequate and well controlled MS trials suggest an increased risk of MS relapse TEAEs among fampridine SR subjects compared to placebo subjects, and the risk increases with increasing dose. Dr. Boehm provided the following table from an analysis requested of Acorda to determine when the relapse AEs occurred during the study. This presentation suggests that the difference between fampridine in placebo is driven by the difference in the post-treatment period when subjects were not taking fampridine SR.

	Placebo Events/N (%)	Placebo Events/Patient years	Fampridine 10mg events/N (%)	Fampridine 10mg events/Patient years
RCTs MS-F202, MS-F203, and MS-F204				
Pre-treatment	0/238 (0)	0/100	6/400 (1.5%)	19.6/100
Double blind	8/238 (3.4%)	15.2/100	16/400 (4%)	17/100

Follow up	1/238 (0.4%)	11/100	6/400 (1.5%)	39.1/100
Open label extension trials MS-F202EXT, MS-F203, MS-F204				
	N/A	N/A	151/660 (22.8%)	14.2/100

Dr. Boehm questions whether the relapses represent a waning drug effect or new neurological deficits that would suggest relapse events. The Division asked the Sponsor to return to the study sties to collect additional information about these events. The Sponsor's response of 8/12/09 was not able to provide information that would allow the Division to answer these questions. In the information that was provided, as discussed in Dr. Boehm's review, examination of walking speed for the 7 fampridine SR 10 mg bid patients with post treatment MS relapse AEs, showed declines that became more pronounced after stopping treatment, although the declines actually began at or prior to visit 5, during active treatment. The data from patients who experienced relapse during the post-treatment phase and who continued in open-label extension phases does not suggest continued increased MS relapse risk among these patients, and there did not appear to be increased MS relapse risk in the extension trial patients compared to controlled trial patients. I agree with Dr. Boehm's suggestion that labeling language and discussion in the Medication Guide could be used to educate patients and physicians about the possibility of worsening symptoms after discontinuing treatment.

Psychiatric AEs – Dr. Boehm notes that there is an increased risk of Psychiatric AEs among fampridine SR treated subjects compared to placebo subjects in the MS adequate and well controlled trials. The risk was driven primarily by increased risk for anxiety and insomnia. The risk appeared to be dose related as shown below as extracted from Dr. Boehm's review.

	Placebo	Fampridine SR 10 mg bid	Fampridine SR 15 mg bid	Fampridine SR 20 mg bid
Anxiety	0.4% (1/238)	1.8% (7/400)	2% (1/50)	3.5% (2/57)
Insomnia	3.8% (9/238)	9.3% (37/400)	18% (9/50)	12.3% (7/57)

This finding was also replicated in the SCI adequate and well controlled trials.

Dr. Boehm also investigated the risk of depression. He found that there did not appear to be differences between fampridine SR and placebo during active treatment periods in adequate and well controlled MS trials, but when examining all TEAEs (on drug and up to 2 weeks following discontinuation) the depression risk for placebo was 0.8% (2/238) compared to 1.3% (5/400 for fampridine SR 10 mg bid, 2% (1/50) for fampridine SR 15 mg bid, and 3.5% (2/57) for fampridine SR 20 mg bid. He reports that for fampridine SR depression AEs occurred during the 14 day follow-up period, after discontinuation of Fampridine SR. None

were SAEs or led to discontinuation. In the SCI trials the risk of depression AEs was 3.1% (7/220) for placebo, 4.9% (12/247) for fampridine SR 25 mg bid, and 0/30 for fampridine SR 40 mg bid. All occurred during active treatment, and 3 led to discontinuation. In the integrated safety database 1 subject committed suicide (described above with deaths), 1 subject with a history of depression and recently diagnosed with renal carcinoma attempted suicide, and 3 subjects (1 with MS and who had a history of depression and suicidal ideation) had AEs of suicidal ideation. A second event of suicidal ideation in the MS population (in a patient who was taking multiple medications including bupropion, escitalopram, and seroquel and who subsequently committed suicide after the Safety Update database lock date) was reported in the Safety update. I agree with Dr. Boehm that there is insufficient evidence to establish a relationship between Fampridine SR and depression AEs.

Urinary Tract Infections – Dr. Boehm notes the risk of UTI AEs among fampridine subjects in controlled trials (both MS and SCI) that exceeded the risk among placebo subjects. In the majority of cases UTI AEs were diagnosed based on symptoms and there was a lack of objective data (urinalysis results, urine culture results) supporting the diagnoses. Dr. Boehm points out that there were not consistent increases in risk among fampridine SR subjects compared to placebo for serious UTIs in MS patients vs SCI patients. When examining AEs from Renal and Urinary Disorders body system group from adequate and well-controlled MS trials, except for urinary frequency and urinary incontinence there is little evidence of disparity of urinary symptoms for fampridine subjects compared to placebo subjects. I agree with Dr. Boehm's suggestion that any future planned fampridine SR trials should attempt to clarify the association between fampridine and UTI that would include collecting cultures and urinalysis in symptomatic patients.

Hepatic Injury Report – Dr. Boehm identified no reports of hepatic injury in the NDA or safety update and no signal for hepatic injury from lab data. However, he has identified a published case of hepatic injury in a patient treated with 4-aminopyridine. This was a 60 y.o. female who developed malaise after 6 months of treatment with 4-aminopyridine (30 mg in 3 daily doses) and 6 weeks after a course of IV steroids for MS. She was found to be slightly jaundiced and had a bilirubin of 33 umol/L (1.9 mg/dL), GGT 199 U/L, AST 359 U/L, and ALT 819 U/L (ALP not reported), and these abnormalities were not present immediately after treatment with steroids. 4-aminopyridine was stopped. The patient reportedly had negative results on serological tests (not specified). Condition improved over the subsequent 3 months with no additional intervention. The information from this case is limited both in details of the case and in allowing other etiologies to be ruled out. I agree with Dr. Boehm that Acorda should closely follow any liver injury cases reported for fampridine SR.

2.3.5 Common Adverse Events

Overall, 93.8% of MS and SCI trial subjects exposed to fampridine SR experienced 1 or more TEAEs, with a similar frequency in the MS controlled and uncontrolled trials. In the adequate and well controlled MS trials, 86.4% (438/507) of fampridine SR subjects experienced one or more AEs compared to 73.5% (175/238) of placebo subjects. Among the most common adverse events (≥ 2%) and at least 2 times greater than placebo in those trials were insomnia, dizziness, headache, asthenia, nausea, balance disorder, paresthesia, back pain, difficulty walking, pharyngolaryngeal pain, gastroenteritis viral, pollakiuria, vomiting, pyrexia, rash, anxiety, and tremor.

Dr. Boehm investigated in more detail dizziness, insomnia, and asthenia. In the MS adequate and well controlled trials, 48 fampridine SR subjects experienced dizziness and the risk increased with dose (7.8%, n=31/400 for 10 mg bid; 20%, n=10/50 for 15 mg bid; and 12.3%, n=7/57 for 20 mg bid). Median time of onset was 12 days, and median duration was 7 days. Dr. Boehm reports that there did not appear to be fampridine-related declines in blood pressure that would explain the increased risk of dizziness, and there did not appear to be an increased risk for syncope for fampridine subjects vs placebo. Dr. Boehm found a greater than expected risk for co-occurrence of balance disorder or fall and dizziness, but that for the 8 patients with co-occurrence, the AEs were contemporaneous for only 4. Similarly, there was a greater than expected co-occurrence of dizziness and fall, but in only 5/16 were these contemporaneous.

The risk of insomnia increased with dose and occurred with a median time to onset of 15 days and a median duration in patients who had resolution reported of 26 days.

Asthenia risk increased with dose. The median time to onset in the 44 fampridine SR subjects in the MS adequate and well-controlled trials was 44.5 days with a median duration of 14 days.

2.3.6 Laboratory findings

Chemistry - Evaluation of mean changes in routine chemistry results from the adequate and well-controlled MS trials were similar for fampridine SR and placebo, except for a larger mean increase in LDH in fampridine SR subjects compared to placebo subjects. Dr. Boehm reports that the difference in LDH appeared to be driven by a large decline in 1 placebo subject. In the SCI adequate and well controlled trials, fampridine subjects experienced a mean increase from baseline of 7.29 compared to 2.76 for placebo (median increase was 6 for fampridine vs 3 for placebo). Chemistry outlier results were similar for fampridine SR and placebo subjects in the MS trials, except for a 2-fold higher risk for phosphorous outliers for fampridine subjects. However, further examination showed that all of the outlier placebo (6/238) subjects had high phosphorous outlier results, whereas 19/507 phosphorous outliers had high outlier results (2.5% vs 3.7%) so that for high outlier results the discrepancy

becomes less. The phosphorous outlier results were not replicated in the SCI trials. In the MS trials (and in the SCI trials) there was a higher risk for sodium outlier results among fampridine subjects (0 for placebo subjects and 6/502 or 1.2% for the MS studies). In the MS studies, 3 fampridine subjects had high elevations and 3 had declines.

There were reportedly no cases in the database of cases of liver injury defined by ALT or AST > 3X ULN AND total bilirubin > 2x ULN. For adequate and well controlled MS trials, no subjects with normal ALT at baseline had on treatment ALT > 3x ULN, with normal AST at baseline had on treatment AST > 3x ULN, or with normal bilirubin at baseline had on treatment bilirubin > 1.5X ULN. In the SCI adequate and well controlled trials, 1 fampridine subject with normal AST at baseline had on treatment AST that was > 3x ULN (< 5x ULN) and one with normal bilirubin at baseline had on treatment bilirubin > 1.5x ULN (< 2x ULN).

Hematology - Hematology mean changes were generally similar for fampridine and placebo in the adequate and well controlled MS studies. In the SCI trials, fampridine SR subjects experienced a slight increase in platelet count (4.66) compared to a slight decline (-1.79) for placebo. Hematology outlier results were similar for fampridine SR and placebo subjects, although fampridine subjects had a higher risk for low hemoglobin outlier results (0.4% for placebo and 1.2% for fampridine SR). This was not replicated in the SCI trials.

Urinalysis – There were no meaningful differences in risk for urinalysis test results when comparing fampridine SR and placebo subjects, and fampridine subjects did not appear to have an increase in urinary leukocytes results in MS trials. Similarly, the adequate and well controlled SCI trials did not have meaningful differences in outlier risk for urinalysis test results when comparing fampridine SR to placebo treated subjects.

2.3.7 Vital Signs

Dr. Boehm reports that there did not appear to be notable mean change vital sign differences between fampridine SR and placebo in the adequate and well controlled MS trials or in the SCI trials. Fampridine SR subjects had slightly higher risk (4.5%) for low systolic blood pressure outliers compared to placebo (2.5%) that was dose related. In the SCI trials the risk for low systolic blood pressure outliers was slightly higher among placebo subjects (16.4%) compared to fampridine subjects (14.8%).

2.3.8 Electrocardiograms

Dr. Boehm reports no meaningful difference in mean change analyses for fampridine SR vs placebo subjects in the adequate and well controlled MS trials when focusing on the change from screen to days 43-119, an on treatment period that included the greatest number of study participants. He reports similar findings for the SCI trials. He did not find a difference in risk for ECG outliers for

fampridine SR compared to placebo. QT results in these trials are shown below, as extracted from Dr. Boehm's review.

	Increase in QT of >30-≤60 msec		Increase in QTc of > 60 msec	
	Placebo	Fampridine SR	Placebo	Fampridine SR
MS trials	3.8% (9/236)	4.6% (23/505)	0.4% (1/236)	(0/505)
SCI trials	5.8% (13/221)	10.4% (28/270)	1.8% (4/221)	3% (8/270)

2.3.9 Special Safety Studies/Clinical Trials

Results of the thorough QT trial was reviewed by the IRT in a memo dated 12/4/08. The trial was performed in 208 healthy subjects who received 5 days of fampridine SR 10 mg bid, 30 mg bid, placebo or moxifloxacin. The 30 mg bid dose was considered to be a supratherapeutic dose as it results in concentrations above those predicted in severe renal impairment where the Cmax is 100% higher compared to normal subjects, according to the IRT's review. The results are shown in the table below as taken from the IRT review, and there is no signal for QT prolongation at the proposed dose.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Fampridine SR (10 mg and 30 mg) and the Largest Lower Bound for Moxifloxacin (FDA Primary Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Fampridine SR 10 mg	0.5	(b) (4)	(-0.5, 7.2)
Fampridine SR 30 mg	0.5		(-1.5, 6.0)
Moxifloxacin 400 mg*	3		(5.9, 13.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points (hours 1, 2, 3, and 4) was 4.9 ms.

2.3.10 Drug Interactions

Dr. Boehm has evaluated drug-demographic interactions and reports that for sex and age, there did not appear to be important differences in risk for all AEs. The relative risk for TEAEs was higher among non-Caucasians than Caucasians, driven by lower risks among the non-Caucasian placebo subjects. This was based on a small number of non-Caucasian subjects (n=37). There were too few non-Caucasians to detect differences in relative risk when stratified by race. Dr. Boehm found that the relative risk for insomnia as well as for balance disorder was higher for females than for males. Dr. Boehm reports that the oldest age group (>65 years) included only 26 fampridine SR subjects and 18 placebo subjects. He reports that subjects 45 to ≥65 years had a higher relative risk for back pain compared to subjects < 45 years old, but for the other TEAEs the risks were similar between the two groups.

For all TEAEs, Dr. Boehm reports that the relative risk for subjects with abnormal renal function was higher than for subjects with normal renal function. For TEAEs occurring in at least 5% of the fampridine SR subjects and at least twice

as commonly compared to placebo, fampridine SR subjects with abnormal renal function had higher risks and relative risks for nausea, balance disorder, dizziness, and insomnia. Because abnormal renal function was considered to include patients with a creatinine clearance of ≤80 ml/min, concerns regarding these findings should also apply to the elderly population and others for whom estimated creatinine clearance is in this range.

Acorda looked for evidence of drug-drug interactions among MS patients considering whether they were taking immune modulators, antispasticity medication, or antidepressants. Dr. Boehm reports that there did not appear to be important differences in relative risks for all TEAEs when comparing subjects taking these medications to those not taking these medications. There did not appear to be an interaction between fampridine and immune modulators for common TEAEs that occurred at least twice as commonly compared to placebo. For antispasticity medications, balance disorder was the only TEAE where the relative risk was higher compared to subjects not using antispasticity medications. For antidepressants, back pain was the only TEAE where this was this case.

2.3.11 Human Carcinogenicity
In the integrated safety database the risk for "neoplasms benign, malignant, and unspecified (incl cysts and polyps)" body system category TEAEs was 2.1% (45/2115). The malignant neoplasms that occurred in more than 1 subject were basal cell cancer (n=10), squamous cell cancer (n=5), breast cancer (n=3), and prostate cancer (n=2). In adequate and well-controlled MS trials there were 3 AES in this category (breast cancer, lentigo, and leiomyoma) and all occurred in the fampridine subjects. In the SCI adequate and well-controlled trials there were 2 TEAEs in this category (lip and or oral cavity cancer, lipoma) and both occurred in fampridine SR subjects. I agree with Dr. Boehm's conclusion that the clinical trial database did not suggest a relationship between fampridine SR and cancer diagnosis but that the safety database is not expected to support a robust assessment of human carcinogenicity.

2.3.12 Human Reproduction and Pregnancy Data
There was 1 pregnancy in the database in a Fampridine SR subject who had her first dose of study medication on 2/8/06. On 4/14/07 she stopped fampridine SR due to the pregnancy. On 4/25/07 she had an ultrasound that estimated gestational age at 7 weeks and 3 days. The patient delivered a full term female and no birth defects were noted.

2.3.13 Overdose, Drug Abuse Potential, Withdrawal and Rebound
Reported symptoms of overdose in the database and in the literature include seizures, vomiting, agitation, tachypnea, diaphoresis, incontinence, hypertension, transient right bundle branch block, PVCs, and accelerated idioventricular rhythm; unusual sensory and behavior symptoms and status epilepticus;

tremulousness, dystonia, choreoathetoid-type movements, fixed stare, facial paralysis, delirium, slurred speech, disorientation, and hypothermia.

With respect to abuse potential, trials in healthy human subjects did not produce stimulant or depressant effects on mood. There were no reports of euphoric mood in the controlled trial patients or in the 1029 MS patients overall, although there were 3 reports of euphoric mood among 704 uncontrolled trial SCI patients and 2 reports in the non-patient safety population. There were several cases of hallucination. The Sponsor states that overdose reports are mostly accidental and that the literature reports of attempted abuse were one-time events that produced acute negative side effects and did not lead to repeated attempts. Abuse potential and dependence potential have not been formally examined.

AEs that occurred after stopping study medication for the adequate and well controlled MS trials and that occurred in at least 1% of fampridine SR subjects and more frequently when compared to placebo were urinary tract infection, MS relapse, balance disorder, difficulty walking, muscle spasticity, cystitis, and upper respiratory tract infection. In the SCI population, these events included constipation, fatigue, oedema peripheral, urinary tract infection, muscle spasms, musculoskeletal stiffness, somnolence, anxiety and decubitus ulcer. There was 1 subject with an AE of drug withdrawal; he was a SCI patient who experienced excess sweating-assoc. withdrawal symptom and this was not an SAE.

2.3.14 Summary of Significant Safety Concerns:
Significant safety concerns are summarized as follows:

- Seizure risk – I agree with Dr. Boehm that fampridine presents a seizure risk, and that the risk at the proposed dose is not well characterized, in part because the population in the clinical trials was highly screened. Risk factors other than dose have not clearly been identified. I agree that the labeling and the medication guide should describe the seizure risk with Fampridine SR. Exposure is increased in the setting of even mild renal impairment, and information on potential risk should be provided in labeling. I agree with contraindication in severe renal impairment. A postmarketing commitment (PMC) should evaluate a lower dose for efficacy; a lower dose would be useful also in patients with renal impairment.
- Urinary Tract Infection – I agree with Dr. Boehm that the risk for urinary tract infection has been poorly characterized and that ongoing or planned clinical trials should incorporate testing to assess the risk.
- Hepatotoxicity – I agree with Dr. Boehm that although there was not a signal for hepatotoxicity in the database, based on the report in the literature, the Sponsor should closely follow-up all reports of liver injury, and should submit any serious liver injury cases as 15-day reports.

2.3.15 Postmarketing Risk Management Plan

Acorda originally submitted a proposed Risk evaluation and Mitigation Strategy (REMS) on 6/22/09 and a revised REMS on 10/19/09. The proposed REMS includes a medication guide and a communication plan. The proposed goal of the REMS is to reduce the potential risk of drug-associated seizures in patients with multiple sclerosis (MS) receiving this drug by: ensuring selection of appropriate patients, promoting informed prescribing, promoting informed use by patients, and utilizing enhanced pharmacovigilance tools. Acorda proposes that fampridine be contraindicated in patients with a history of seizure and in patients with severe renal impairment. At the time of writing of this review, the REMS review has not been completed.

2.3.16 Conclusions

Dr. Boehm has identified the safety issues associated with fampridine use, including the increased risk for seizures that appears to be dose-related. The risk has not been well characterized, even at the proposed 10 mg dose, in a broad population because the clinical trials population was highly selected. The risk of seizures should be described in the labeling and addressed in a medication guide as a component of a REMS. A signal for urinary tract infection should be further characterized in ongoing or planned clinical trials. There has been a case report of hepatotoxicity described in the literature, and further reports of hepatotoxicity will require follow-up. A lower dose should be evaluated as a PMC. The proposed REMS requires review.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY U YASUDA
11/30/2009

CLINICAL SAFETY REVIEW

Application Type	NDA
Application Number(s)	022-250
Priority or Standard	Priority
Submit Date(s)	4/22/09
Received Date(s)	4/22/09
PDUFA Goal Date	10/22/09
Division / Office	DNP/ODE 1
Reviewer Name(s)	Gerard Boehm, MD, MPH
Review Completion Date	10/19/09
Established Name	Fampridine SR
(Proposed) Trade Name	Pending
Therapeutic Class	Potassium Channel blocker
Applicant	Acorda Therapeutics
Formulation(s)	Controlled release tablet
Dosing Regimen	10mg BID
Indication(s)	Improvement of Walking Ability
Intended Population(s)	Multiple Sclerosis Patients

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Review of Safety

Safety Summary

This review considers the safety data for Fampridine SR as presented in Acorda's NDA 022-250. Fampridine SR is an orally administered, controlled release dosage form of 4-aminopyridine, a selective blocker of potassium channels. In addition to its proposed use as a therapeutic agent, 4-aminopyridine is used as a bird poison (trade names Avitrol 200 and Avitroland, classified by the EPA as a Restricted Use Pesticide) and as a research tool to characterize potassium channels

4-aminopyridine improves conduction in demyelinated nerve fibers and has been used to improve symptoms in multiple sclerosis (MS) patients. Since no dosage forms of 4-aminopyridine are currently approved for use, MS patients have depended on compounding pharmacies to obtain the drug. This has resulted in reports of toxicity related to compounding errors. The most concerning toxic effect of 4-aminopyridine is seizure. To limit seizure risk, the Fampridine SR formulation was developed and Acorda intends to limit recommend Fampridine SR doses to 10mg bid.

Clinical studies of 4-aminopyridine have been conducted by several different sponsors examining its use in various indications including MS, spinal cord injury (SCI), and Guillain-Barre Syndrome. Acorda became the sponsor for Fampridine SR in 1998 and conducted phase III trials in MS patients for the indication of improving walking ability. There are several FDA approved treatments for MS but Fampridine SR would be the first approved treatment for improvement of walking ability in MS patients.

The Fampridine SR NDA submission summarizes pooled safety data from 45 trials including 2,115 subjects from studies in healthy volunteers and adults with MS and SCI. Acorda provided additional safety data for 138 subjects from 11 trials that could not be pooled due to lack of available datasets from previous IND holders. The overall pool of safety data includes information collected from MS subjects (clinical pharmacology, controlled, and uncontrolled trials), SCI subjects (clinical pharmacology, controlled, and uncontrolled trials), and non-patient subjects (healthy volunteers, volunteers with renal deficiency). Acorda also presents safety data using subsets of the pooled data. Acorda presents results for MS subjects and SCI subjects (clinical pharmacology, controlled, and uncontrolled trials n=1510). Acorda presents separately results for only MS subjects (n=917), only SCI subjects (n=583) and only non-patient subjects (n=382). In addition, Acorda presents comparative results from MS adequate and well controlled trials (Fampridine SR n=507, placebo n=238), and from SCI adequate and well controlled trials (Fampridine SR n=277, placebo n=229). Lastly, Acorda provides summaries of

safety data for the 11 trials excluded from the pooled analysis. For overall event risk estimates, this review relied on the analyses of the pooled safety population for MS subjects and SCI subjects. For comparative risk analyses, this review primarily relied on data from the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204).

The number of patients exposed to Fampridine SR in the NDA trials exceeds ICH guidelines and investigators exposed adequate numbers of subjects to the intended recommended dose (10 mg bid). The Fampridine SR NDA submission includes safety data for 2253 subjects. Acorda reported that 1,621 subjects were exposed to at least one dose of Fampridine SR, including 807 MS subjects. In the NDA submission, 780 subjects were exposed to Fampridine SR for at least 6 months (601 MS subjects) and 444 were exposed for at least 1 year (405 MS subjects). The majority of subjects were exposed to Fampridine SR doses of at least 10mg bid.

I identified no significant deficiencies in the NDA safety submission. Acorda submitted all necessary summaries and supporting data. There were no notable inconsistencies between the data sources. The routine clinical safety testing in the fampridine MS trials seemed appropriate and capable of identifying major safety signals with Fampridine SR. The Fampridine SR NDA included instances of coding inadequacies, but none are expected to impact our understanding of the safety profile of Fampridine SR.

Deaths occurred infrequently in the Fampridine SR clinical trials and there did not appear to be clusters of unusual causes of death. The reported causes of death for Fampridine SR clinical trial subjects were oxycodone overdose, aortic dissection, suicide, unknown/found dead in bed, intracerebral hemorrhage, and fall (positional asphyxia).

15.1% (228/1510) of MS and SCI subjects experienced one or more serious adverse events (SAEs). The System Organ Class (SOC) groupings with the most SAEs were Nervous system disorders (5.4%, 81/1510), and Infections and Infestations (4.3%, 65/1510). No subjects experienced SAEs of hepatic failure, hepatitis, rash, Stevens Johnson syndrome, Toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, or aplastic anemia. The most commonly reported SAEs were multiple sclerosis relapse (2.5%), convulsion (1.3%), urinary tract infection (1.2%), and cellulitis (1.1%). In the MS adequate and well controlled trials, SAEs were 3 times more frequent among Fampridine SR subjects (6.5%, 33/507) compared to placebo subjects (2.1%, 5/238) and the risk for all SAEs among Fampridine SR subjects appeared dose related. Multiple sclerosis relapse was the only SAE that occurred in more than 2 Fampridine SR subjects (Fampridine SR n=7, 1.4%; placebo n=0).

14.6% of MS and SCI subjects experienced one or more AEs leading to discontinuation. The most common AEs leading to discontinuation among Fampridine SR subjects in the pool of MS and SCI study subjects were dizziness (2.5%), insomnia (1.5%), convulsion

(1.3%), asthenia (1.3%), nausea (1.1%), anxiety (1.1%), and paresthesia (1.0%). In the MS adequate and well controlled trials, 3.4% (17/507) of Fampridine SR subjects had one or more AEs leading to discontinuation compared to 2.1% (5/238) of placebo subjects. The AEs leading to discontinuation of at least 2 Fampridine SR subjects and that led to discontinuation more frequently compared to placebo were headache (Fampridine SR 0.8%, 4/507; placebo 0/238), balance disorder (Fampridine SR 0.6%, 3/507; placebo 0/238), dizziness (Fampridine SR 0.6%, 3/507; placebo 0/238), and confusional state (Fampridine SR 0.4%, 2/507; placebo 0/238).

Common AEs that occurred more frequently among Fampridine SR MS subjects and in some cases that exhibited evidence of a dose response relationship included urinary tract infection. insomnia, dizziness, headache, asthenia, nausea, fatigue, MS relapse, balance disorder, paresthesia, back pain, muscle spasms, nasopharyngitis, constipation, diarrhea, difficulty walking, pharygolaryngeal pain, gastroenteritis viral, pollakiuria, vomiting, pyrexia, rash, anxiety, cough, and tremor.

As noted above, Fampridine SR causes seizures and Acorda evaluated the seizure risk at the dose intended for the treatment of MS patients (10mg bid). Data from the controlled clinical trials at the 10mg bid dose did not suggest a difference in seizure risk compared to placebo but this comparison relied on only 400 Fampridine SR treated patients, 238 placebo patients and only 2 seizure events (1 Fampridine SR, 1 placebo). In these same studies, at 20mg bid (only a doubling of the dose intended to be marketed), the seizure risk was 10-fold higher (based on 2 events in 57 subjects), a concerning finding suggesting a narrow therapeutic index. In the open label trials, the seizure risk in those treated with 10mg bid was similar to the risk seen in the Fampridine SR subjects treated with 10mg bid during controlled trials. The results from this open label population must be considered very carefully since this was a highly selected population. These patients were screened by history and EEG prior to the RCT, those with exposure to Fampridine SR in the RCT (roughly 2/3 of open label trial participants) survived a trial of therapy without seizure, and then all subjects were screened with EEG again prior to entering the open label trial.

Comparing the seizure risk in the Fampridine SR clinical trial population with background data or data from other MS drug development programs must also be viewed with caution. The screening in the Fampridine SR trials and usual concerns about potentially important differences among the Fampridine SR population and the general MS background population or other drug development program populations make these comparisons problematic.

The current evidence supports a dose-related risk of seizure with Fampridine SR, with limited experience at the dose intended for treatment, and some evidence of increasing risk just above the therapeutic dose. If the risk benefit for Fampridine SR is favorable and the drug is approved, Fampridine SR should not be used in patients with seizure history and prospective patients should be screened with EEG prior to treatment, the

conditions of use in the clinical trials. Fampridine SR labeling should include information about the potential for increased seizure risk at the intended dose, should strongly warn about not increasing the dose above the recommended dose and urge caution in patients at risk for higher exposures (ex. renal insufficiency). A Medication Guide should explain the risk for patients and include information cautioning against increasing the dose.

Results from the pooled analysis of AEs from the adequate and well controlled MS trials demonstrated an increased risk of multiple sclerosis relapse TEAEs among Fampridine SR subjects compared to placebo subjects and the risk among Fampridine SR subjects increased with increasing dose. The difference in MS relapse risk between Fampridine SR and placebo in the RCT study data was driven by differences in the post- treatment period, when subjects were not taking Fampridine SR. The post treatment phase was short in duration (only 2 weeks) meaning that this finding is based on very limited observation time. Also complicating this assessment is the suggestion of differences between the placebo and Fampridine SR groups based on the pre-treatment, baseline data. The MS relapse risk in the Fampridine SR group prior to initiating treatment was 4-fold higher (30.3/100PY) than the risk in the placebo group during the pre-treatment phase (7.3/100PY).

The reason for the observed difference in MS relapse risk between Fampridine SR subjects and placebo subjects is not clear. Acorda's explanation, that the MS relapse TEAEs represent a waning therapeutic effect following discontinuation seems to be a reasonable explanation. Unfortunately the available data presented in the narratives for these events are not sufficient to allow differentiation between waning therapeutic effect and relapse of the MS disease process. In fact, in some cases, these events appeared to be true relapses to clinicians because the events resulted in hospitalization and treatment with steroids.

The data from patients who experienced relapse during the post treatment phase and who continued in open label extension phases is reassuring. These data did not suggest continued increased MS relapse risk among these patients. Furthermore, there did not appear to be increased MS relapse risk in the extension trial patients compared to the RCT patients.

Acorda suggests that patients and physicians should be counseled to expect the possibility of worsening MS symptoms after discontinuing treatment. Acorda did not suggest how this might be accomplished. Labeling language and discussion in the Medication Guide could accomplish this goal.

The AE data from the Fampridine SR clinical trials (both MS and SCI) suggested an increased risk for urinary tract infections in Fampridine SR patients compared to placebo patients. In many cases, these events were diagnosed based only on symptoms and UA and/or urine cultures were not performed. There did not appear to be

consistent increases in risk among Fampridine SR subjects compared to placebo subjects for UTI SAEs (elevated risk in Fampridine SR MS patients, but not in SCI Fampridine SR patients). There is insufficient evidence to evaluate Acorda's hypothesis that these UTI events represent drug related sensory symptoms rather than actual infections. Any future planned Fampridine studies should attempt to clarify the association between Fampridine and UTI, perhaps by questioning all study patients about urinary symptoms and collecting cultures and UAs in symptomatic patients.

Lab data, vital sign data and ECG data collected during the clinical trials did not find evidence of Fampridine SR related deleterious effects. A formal QT study did not find evidence of QT prolongation in subjects exposed to Fampridine SR.

Problem List/Recommendations
Labeling and the Medication Guide should describe the seizure risk with Fampridine SR. In accordance with the Advisory Committee vote, the labeling should not require EEG testing prior to use, but Fampridine SR should not be used in patients with a history of seizure. Fampridine SR should be contraindicated in moderate and severe renal insufficiency and all patients should undergo measurement of creatinine clearance prior to starting treatment.

Acorda should study Fampridine SR doses <10mg bid.

Any ongoing or planned fampridine clinical trials should incorporate testing to assess the risk for UTIs in Fampridine SR treated patients.

Acorda should closely follow up all reports of liver injury. Follow up should include complete description of the case, outcome information, lab test results, biopsy results, and post mortem test results. In addition, Acorda should submit any serious liver injury cases as 15-day reports.

Acorda should incorporate the labeling language that will be requested by the Division.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Acorda reported that 2253 subjects participated in the 56 clinical trials included in the Fampridine SR NDA (cutoff date 7/31/08). The Fampridine SR integrated safety database included 2115 subjects from 45 trials. Acorda could not include the remaining 138 subjects from 11 trials in the integrated safety database because they were unable to obtain from former IND holders the SAS data sets used as the basis for the

integrated review (Summary of Clinical Safety, p.9). Acorda summarized separately the safety data for these 138 subjects not included in the integrated safety database.

Investigators collected safety data during trials that evaluated various fampridine treatment indications including multiple sclerosis, spinal cord injury (SCI), and Guillain-Barre syndrome as well as during clinical pharmacology trials. The integrated safety database includes 382 healthy volunteers from 13 trials, 1029 subjects from 20 trials in MS patients, and 704 subjects from 12 trials in SCI patients (Summary of Clinical Safety, Table 1, p.12).

Acorda identified 1922 subjects exposed to one or more doses of fampridine (all formulations). Acorda summarized the exposure by indication in table 2 and I reproduce that table below.

Total Number of Patients Exposed to Fampridine and Placebo in all Clinical Trials

				First Use of Fampridine		
Trial Population	Trial Category	Trial Number	Placebo	Fampridine SR	Fampridine Other	Fampridine Total
Multiple Sclerosis	Clinical Pharmacology	All	56	67	89	145
	Placebo Controlled	All	330	532	89	621
	Uncontrolled	All		208		974
		Total	*386*	*807*	*178*	*974*
Spinal Cord Injury	Clinical Pharmacology	All		14	4	18
	Placebo Controlled	All	322	372		372
	Uncontrolled	All		203		203
		Total	*322*	*589*	*4*	*593*
Renal Deficiency	Clinical Pharmacology	RD10F-SR012004		20		20
Guillain-Barre	Guillain-Barre	CGBS Phase 2A#	7		8	8
		CGBS Phase 2B#	17		16	16
Healthy Volunteers	Clinical Pharmacology	All	113	205	147	311
All	*All*	*Total from all studies*	*797*	*1621*	*224*	*1793*

		with available data				
		Grand Total	**845**	**1621**	**353**	**1922**

Acorda's Safety Update (submitted on 6/22/09 with a data cutoff date of 11/30/08) included additional safety data for subjects continuing in ongoing MS extension trials (MSF-202 EXT, MSF-203 EXT, and MSF 204 EXT) and data for 30 subjects that participated in a newly completed PK study.

7.1.2 Categorization of Adverse Events

Acorda defined adverse events (AEs) as "any untoward medical occurrence in a clinical investigation patient that did not necessarily have a causal relationship with treatment." Acorda defined treatment emergent adverse events (TEAEs) as "AEs with the date of onset (or worsening severity) on or after the start of double-blind/active study medication and no more than 14 days after the last dose of study medication." In addition to providing analyses of TEAEs, Acorda provided additional analyses that examined TEAEs that occurred during active treatment and TEAEs that occurred during follow up (after treatment cessation).

In addition to the routine exploration of AEs, Acorda presented additional analyses of selected AEs of particular concern. Acorda considered seizures AEs of special interest because of the known causal association with fampridine. Following discussions with the Division, Acorda agreed to classify all seizure AEs as SAEs (Summary of Clinical Safety, p.22). Acorda coded AEs involving focal or generalized, grand mal type motor seizures that were often not well described by observers to the MedDRA term "convulsion". Four events reported as complex partial seizures were coded directly to the MedDRA term "complex partial seizures" and one event that Acorda considered severe and prolonged was coded to the MedDRA term "grand mal convulsion" (Summary of Clinical Safety, p.40). For a separate analysis, Acorda also pooled and analyzed AE terms that could be a response to underlying seizure activity. I list those AE terms are listed below:

> Abnormal dreams, Agitation, Aphasia, Aphonia, Asthenia, Clonus, Cognitive disorder, Complex partial seizure, Confusional state, Convulsion, Daydreaming, Delirium, Delusion, Depressed level of Consciousness, Disorientation, Dissociation, Disturbance in attention, Dizziness, Encephalopathy, Hallucination, Hallucination auditory, Hallucination visual, Hypersomnia, Insomnia, Lethargy, Listless, Loss of consciousness, Mania, Memory impairment, Mental impairment, Mental status changes, Muscle contractions involuntary, Myoclonus, Nausea, Neurologic symptom, Nightmare, Panic attack, Paralysis, Parosmia, Psychomotor hyperactivity, Psychotic disorder, Seizures, Sensory disturbance, Somnolence,

Suicidal ideation, Syncope, Tension, Thinking abnormal, and Transient ischemic attack (ISS Statistical Plan, p.34).

Acorda compared the frequency of the pool of these potential seizure AE terms for Fampridine SR and placebo.

In addition to seizures, Acorda analyzed the following AEs as AEs of special interest: other CNS AEs not characterized as seizures; psychiatric disorders; suicidal ideation and related events; MS relapse; urinary tract infections; injury, poisoning and procedural complications; and infections and infestations.

Coding Dictionary Evaluation
Adverse event verbatim terms were initially coded to either COSTART or MedDRA. The NDA safety analyses are based on AE terms that were ultimately coded to MedDRA Version 8.1 (Clinical Summary of Safety, p.22). Adverse events were voluntarily reported by trial subjects in response to the investigator's question regarding how the subject was feeling since the last visit and study protocols did not use checklists of potential AEs (ISS, p.133).

Coding the various AE verbatim terms reported by study subjects (ex. "my stomach hurts") to specific preferred terms (ex. abdominal pain) is an important task that allows for the analysis of AEs occurring during drug development programs. The output of the coding process must be evaluated for results that might hamper AE risk evaluation such as lumping unrelated events under single preferred terms, splitting similar events into multiple terms or coding events to preferred terms so vague that they have limited value. Such occurrences can be present in any NDA, usually with little consequence, but it is important to look for coding inadequacies that could impact the safety assessment.

The Fampridine SR NDA included instances of coding inadequacies, but none are expected to impact our understanding of the safety profile of Fampridine SR. I identified occasional examples of lumping unrelated AE terms into single preferred term. For example, the MedDRA term bacterial infection subsumed a collection of verbatim terms so diverse (bacterial infection in toenail, bacterial infection of stomach, left elbow infection) as to render the preferred term unhelpful. The Fampridine SR NDA also included instances where similar events were split into different preferred terms. For example, Acorda coded similar clinical events to the preferred terms cystitis, urinary tract infection, Escherichia urinary tract infection, and kidney infection. To take into account this coding approach, I conducted additional analyses by pooling these different preferred terms to assess urinary tract infection risk. Acorda used a number of preferred terms that were unhelpful in terms of describing the events they subsumed. Examples of unhelpful preferred terms include eye disorder, bladder disorder, liver disorder, hypersensitivity, feeling abnormal, and mental impairment. Assessing vague preferred term AEs requires examining the verbatim terms along with the preferred terms.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Acorda provides various pools of data to summarize the safety experience with Fampridine SR. The overall pool of safety data includes information collected from MS subjects (clinical pharmacology, controlled, and uncontrolled trials), SCI subjects (clinical pharmacology, controlled, and uncontrolled trials), and non-patient subjects (healthy volunteers, volunteers with renal deficiency). Acorda also presents safety data using subsets of the pooled data. Acorda presents results for MS subjects and SCI subjects (clinical pharmacology, controlled, and uncontrolled trials n=1510). Acorda presents separately results for only MS subjects (n=917), only SCI subjects (n=583) and only non-patient subjects (n=382). In addition, Acorda presents comparative results from MS adequate and well controlled trials (fampridine n=507, placebo n=238), and from SCI adequate and well controlled trials (fampridine n=277, placebo n=229). Lastly, Acorda provides summaries of safety data for the 11 trials excluded from the pooled analysis. For overall event risk estimates, this review will rely primarily on the analyses of the pooled safety population for MS subjects and SCI subjects. For comparative risk analyses, this review will primarily rely on data from the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204). This review will present data from other sub-groupings for specific safety issues, for clarification, or for further exploration of risk.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The number of subjects exposed to fampridine in the development program exceeds the subject exposure recommendations in the ICH guidance document.

In the entire development program, 1922 subjects received at least one dose of fampridine (1793 in the integrated safety database and 129 from trials not included in the integrated safety database). This total includes 1621 subjects that were exposed to Fampridine SR, the formulation Acorda intends to market. For the population with the indication being considered for approval, subjects with MS, Acorda exposed 917 subjects to fampridine (807 to SR formulation). The following table summarizes exposure by formulation, for MS subjects, and by duration, through the NDA cutoff date.

Exposure groups	Number exposed to all fampridine formulations	Number exposed to fampridine SR
Total exposed	**1922**	**1621**
Integrated database	1793	1621
MS subjects	*917*	*807*

Non-integrated	129	0
MS subjects	*57*	*0*
Exposed>=6months	**792**	**780**
Integrated database	792	780
MS subjects	*601*	*601*
Non-integrated	0	0
Exposed>=1 year	**456**	**444**
Integrated database	456	444
MS subjects	*405*	*405*
Non-integrated	0	0

Demographics
Acorda provided tables that summarized the demographic factors for the MS patients that participated in clinical trials. Below, I summarize demographic data for the adequate and well controlled MS trials that served as the basis for the majority of comparative analyses in the NDA safety data presentations.

Demographic Factors for Subjects in the Adequate and Well Controlled MS Trials MS-F202, MS-F203, and MS-F204

Demographic Factor	Placebo	Fampridine SR			
	(n=238)	10mg bid (n=400)	15mg bid (n=50)	20mg bid (n=57)	Total (n=507)
Age (years)					
Mean	51.1	51.7	47.8	52.3	51.4
Median	51	53	47	53	52
Min, Max	24, 70	25, 73	30, 66	29, 67	25, 73
Sex					
Male	94 (40%)	114 (29%)	16 (32%)	23 (40%)	153 (30%)
Female	144 (60%)	286 (71%)	34 (68%)	34 (60%)	354 (70%)
Race					
Caucasian	216 (91%)	374 (94%)	44 (88%)	52 (91%)	470 (93%)
Black	14 (6%)	15 (4%)	3 (6%)	3 (5%)	21 (4%)
Asian	1 (<1%)	3 (<1%)	1 (2%)	0	4 (<1%)
Other	7 (3%)	8 (2%)	2 (4%)	2 (4%)	12 (2%)

From Table 4, Summary of Clinical Safety, p18)

There was a slightly higher percentage of females in the Fampridine SR group compared to the placebo group, but there did not appear to be meaningful differences in age or race between the treatment groups.

Acorda reported that for the Fampridine SR treatment group 27% of subjects were classified with relapsing remitting MS, 16% with primary-progressive MS, 54% with secondary progressive MS, and 3% with progressive relapsing MS. For the placebo group, 31% were classified with relapsing remitting MS, 20% with primary progressive MS, 48% with secondary progressive MS, and 2% with progressive relapsing MS (ISS Table 39).

In the following table, I summarize demographic data for MS patients that participated in clinical pharmacology trials and in the uncontrolled MS trials.

Demographic Factors for Subjects in Clinical Pharmacology Trials and in the Uncontrolled MS Trials

Demographic factor	Clinical Pharmacology Trials (Duration 1 week or less) (N=94)	Uncontrolled Trials (Duration > 1 week) (n=693)
Age (years)		
Mean	46.6	51.7
Median	47	51
Min, Max	23, 64	25, 71
Sex		
Male	38 (40%)	321 (35%)
Female	56 (60%)	454 (65%)
Race		
Caucasian	90 (96%)	655 (95%)
Black	0	21 (3%)
Asian	1 (1%)	4 (<1%)
Other	3 (3%)	9 (1%)

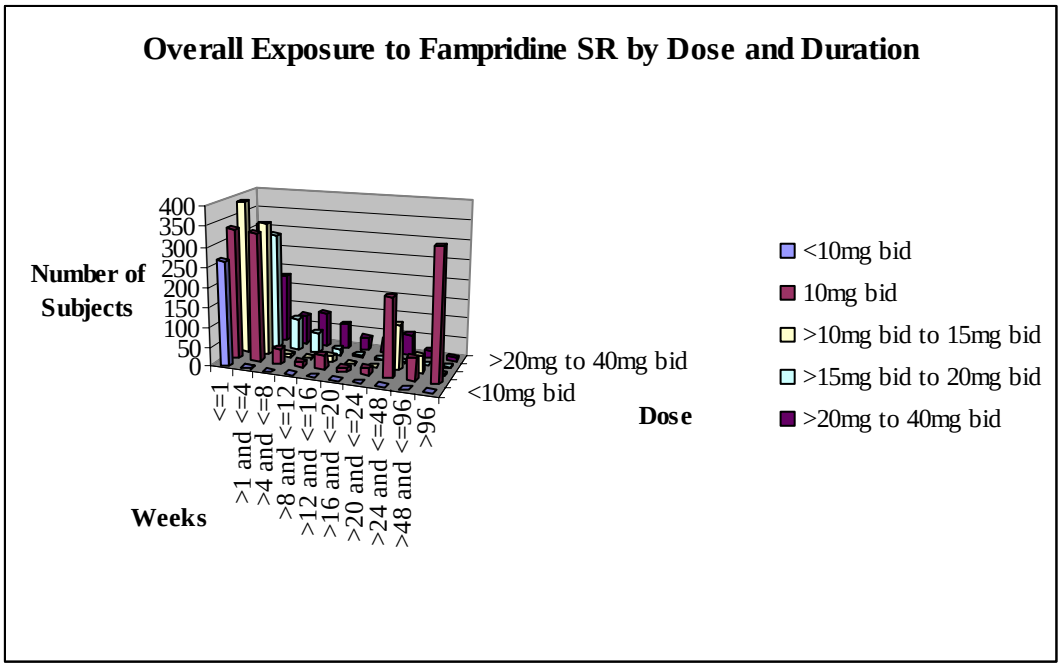
From ISS table 2.2.1

In the uncontrolled trials, Acorda reported that 26% of subjects were classified with relapsing remitting MS, 14% with primary-progressive MS, 50% with secondary progressive MS, and 3% with progressive relapsing MS (7% missing MS diagnosis type information) (ISS Table 40).

7.2.2 Explorations for Dose Response

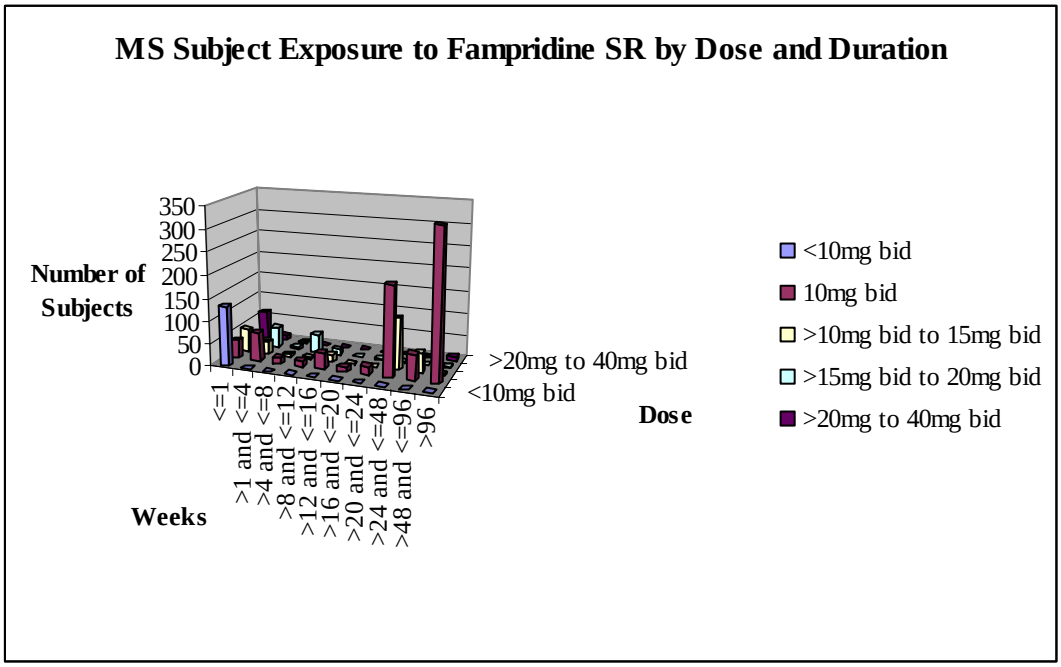
Exposure by Dose
Acorda's ISS Table 7.0.1 summarizes the number of subjects exposed to the different doses used in the Fampridine SR development program trials. Table 7.0.1 demonstrates that most study subjects in the Fampridine SR development program were exposed to Fampridine SR doses ≥10mg bid. Acorda's proposed labeling for Fampridine SR recommends a dose of 10mg bid.

Exposure by Dose and Duration
Acorda's ISS Table 7.0.2 summarizes exposure to Fampridine SR by dose and duration. I used the data from Table 7.0.2 to create the following graphs depicting exposure by dose and duration for the Overall population and the MS population.



This graph demonstrates that Acorda exposed most subjects to Fampridine SR doses of 10mg bid or greater with a number of subjects exposed more than 26 weeks.

The following graph summarizes exposure to Fampridine SR in MS trials included in the integrated safety database.



This graph demonstrates that most MS subjects were exposed to the 10mg bid dose and that a considerable number of subjects were exposed for more than 48 weeks. Few MS patients were exposed to Fampridine SR doses above 10mg bid.

7.2.3 Special Animal and/or In Vitro Testing

Acorda reported results of animal trials assessing the risk and mechanism of seizures. In addition, Acorda provide results from hERG channel testing, action potential testing in isolated dog Pukinje fibers, and cardiovascular effect observations in beagles. These data are examined in the Preclinical pharmacology section 4.3 of the NDA review.

7.2.4 Routine Clinical Testing

The routine clinical safety testing in the Fampridine SR MS trials seemed appropriate and capable of identifying major safety signals. In the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204), at each visit, subjects underwent AE assessment, physical exam, and vital signs testing, and at multiple visits, subjects underwent laboratory testing and ECG testing. These trials required follow-up visits up to 2 weeks after stopping Fampridine SR that allowed for assessment for potential late-occurring AEs and for withdrawal symptoms that could manifest following treatment cessation. In the open label extension trials (MS-F202EXT, MS-F203EXT, and MS-F204EXT) for the above RCTs, subjects were screened and then began treatment within 2 weeks of screening. Subjects were followed initially at 2 week intervals, with subsequent increases in interval of follow up. Subjects were ultimately seen in by

investigators at 26 week intervals with phone call follow up between clinic visits. Subjects were also seen for a follow up visit (up to 4 weeks after completing treatment). Subjects' safety assessments during these open label extension trials included AE assessments, physical exams, vital signs, lab testing, and ECGs.

7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor's in vitro and in vivo testing for fampridine metabolism, clearance and interactions seemed appropriate. Acorda found that Fampridine SR absorption was 96% and that 90% is excreted unchanged in urine. CYP2E1 is the major enzyme responsible for 3-hydroxylation of metabolized Fampridine SR. There were no identified inhibitors or inducers and fampridine is not an inhibitor or inducer of P450s. Fampridine SR is not a P-glycoprotein substrate or inhibitor. The half-life of Fampridine SR was 5.2-6.5 hours. Fampridine SR can be taken with or without food. Acorda found no evidence of drug-drug interactions with either baclofen or betaseron. Details of these assessments can be found in the Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Fampridine is a new molecular entity and does not belong to an approved class of drugs.

7.3 Major Safety Results

7.3.1 Deaths

Deaths occurred infrequently in the Fampridine SR clinical trials and there did not appear to be clusters of unusual causes of death.

Acorda reported six deaths that occurred within 30 days of last exposure to Fampridine SR during the clinical trials included in the integrated safety database. Five of these deaths were MS trial subjects and 1 was a SCI trial subject. One additional death (in an MS trial subject) occurred 5 weeks after last Fampridine SR exposure. Acorda also identified one death in a subject receiving placebo (SCI trial).

Five of the six deaths within 30 days of last Fampridine SR dose occurred in MS trial subjects (ISS, pp. 212-213). All five of these deaths occurred during open label extension phases of trials. The reported causes of death for these five trial subjects were oxycodone overdose, aortic dissection, suicide, unknown/found dead in bed, and intracerebral hemorrhage. Four of the 5 MS trial subjects that died within 30 days of last fampridine exposure were taking 10mg bid Fampridine SR doses at the time of death and one was taking 15mg bid. I summarize details for these five deaths below.

Subject 10001 in trial MS-202 EXT was a 57 year old female and was receiving Fampridine SR 10 mg bid. dose at the time of her death. She had been treated with Fampridine SR for almost 3 years at the time of her death. The patient's partner found her in bed and extremely lethargic. She became unresponsive and was transferred to the hospital where she was pronounced dead. Autopsy revealed that the patient died of accidental oxycodone toxicity. The narrative did not explain why this subject was taking oxycodone.

Subject 21007 in trial MS-F202 EXT was a 58 year old female and was receiving Fampridine SR 15 mg bid prior to death. She had been treated with Fampridine SR for approximately 3 weeks, and then stopped the medication after developing neck pain. Four days later she presented to the ER with complaint of neck pain. She experienced cardiopulmonary failure upon presentation. A CT scan revealed a ruptured aorta. During corrective surgery for the dissection, the patient experienced bleeding and hypoxia and developed several large cerebral infarcts. The patient died ten days after presenting to the ER. The patient had a history of elevated cholesterol and was taking atorvastatin (screening cholesterol 182mg/dL). Her screening blood pressure was 150/96mmHg and her on treatment blood pressure recorded in the CRF was 130/94mm Hg at her 2 study visits. The subject's internist prescribed atenolol for hypertension 5 days before the subject presented to the ER with aortic dissection but there is no information about the subject's blood pressure results that prompted her internist to start treatment.

Subject 220011 in trial MS-203 EXT was a 65 year old male who was receiving Fampridine SR 10 mg bid at the time of his death. The subject committed suicide by self-inflicted shotgun wound of the head, which was the immediate cause of death. The patient's wife had died one week prior to the subject's suicide.

Subject 34011 in trial MS-F203 EXT was a 45 year old female who was receiving Fampridine SR 10 mg bid at the time of her death. She had been treated with Fampridine SR for over 2 years. The patient retired to bed for the evening and was found deceased the next morning. According to the patient's family, she had expressed feeling tired and unwell at times since her MS diagnosis. The family requested there be no autopsy; therefore, the patient's cause of death is not known. The subject had a history of elevated cholesterol. She was taking a number of concomitant medications prior to death including atorvastatin, pinaverium (CCB for irritable bowel), tizanidine, citalopram, oxycontin, gabapentin, baclofen, amitriptyline, rabeprazole, clonazepam, nortriptyline, botulinum toxin, methylprednisone, ondansetron, and mitoxantrone. Adverse events reported during the trial included injuries from falls, MS exacerbation, difficulty sleeping, indigestion, upper respiratory infections fatigue, and feeling unwell.

> Subject 35001 in trial MS-F203 EXT was a 51 year old male receiving Fampridine SR 10 mg bid at the time of his death. The subject had been treated with Fampridine SR for over a year when he presented to the emergency room after taking a dose of alprostadil for impotence. At an unknown time, he was unresponsive and his right eye was severely dilated at which time emergency services were called. Upon arrival to the ER, a CT scan was performed showing a "major hemorrhage". The subject died the following day due to an intracranial hemorrhage caused by a brain aneurysm. The subject had a history of hypertension and was treated with lisinopril. *Note this death was included in the ISS but not in the Summary of Clinical Safety

The death in the spinal cord injury patient within 30 days of last Fampridine SR exposure involved subject 03B10 in trial SCI-F201EXT. This 57 year old male was receiving Fampridine SR 40 mg bid prior to death. The subject was found dead on the floor in front of his wheelchair on his face and knees with his arms by his sides. His fall from the wheelchair resulted in positional asphyxia (compressed airway) which led to death. Acorda reported that no autopsy was performed.

The death in the MS subject that occurred 5 weeks after last Fampridine SR exposure (Subject 009/004, trial MS-F203) involved a 52 year old male and the cause of death documented by autopsy was ischemic and hypertensive heart disease. This subject had a history of smoking, hypertension and elevated triglycerides. Acorda noted that fampridine plasma concentration data collected at the two-week follow-up visit after completing the trial did not show detectable fampridine levels.

The death in the placebo subject (10119, Trial SCI-F302) was attributed to atherosclerotic disease complicated by morphine intoxication.

No deaths were reported from the fampridine trials excluded from the integrated safety analysis.

In the Safety Update, Acorda reported one addition death from an ongoing MS trial. I summarize that death below.

> Subject 03001 from trial MS-F202 EXT was a 68 year old female receiving Fampridine SR 10 mg bid prior to death. The subject had been treated with Fampridine SR for over 4 years. She was found unresponsive by her husband. She was taken to a hospital by ambulance and was pronounced dead. She was diagnosed with an intracranial hemorrhage and no autopsy was performed.

7.3.2 Nonfatal Serious Adverse Events

MS and SCI Trials Pooled

Acorda reported that 15.1% (228/1510) of Fampridine SR MS and SCI subjects experienced one or more SAEs. The System Organ Class (SOC) groupings with the most SAEs were Nervous system disorders (5.4%, 81/1510), and Infections and Infestations (4.3%, 65/1510). No other SOC grouping of SAEs included >1% of subjects. In the table below, I identify the SAEs reported by at least 3 subjects in MS and SCI trials.

Serious Adverse Events Reported by at Least 3 Fampridine subjects in MS and SCI Trials

SAE Preferred Term	N (%)
Multiple sclerosis relapse	38 (2.5%)
Convulsion	19 (1.3%)
Urinary tract infection	18 (1.2%)
Cellulitis	16 (1.1%)
Pneumonia	13 (0.9%)
Sepsis	7 (0.5%)
Muscle spasticity	5 (0.3%)
Pulmonary embolism	4 (0.3%)
Deep venous thrombosis	4 (0.3%)
Nausea	4 (0.3%)
Asthenia	4 (0.3%)
Fall	4 (0.3%)
Anemia	3 (0.2%)
Atrial fibrillation	3 (0.2%)
Chest pain	3 (0.2%)
Influenza	3 (0.2%)
Urosepsis	3 (0.2%)
Hip fracture	3 (0.2%)
Osteoarthritis	3 (0.2%)
Breast cancer	3 (0.2%)
Complex partial seizures	3 (0.2%)
Encephalopathy	3 (0.2%)
Syncope	3 (0.2%)
Anxiety	3 (0.2%)
Decubitus ulcer	3 (0.2%)

Source: ISS Table 28.1.1a

In addition to the more frequently reported SAEs listed above, 1 subject experienced an SAE of pancytopenia and 1 subject experienced an SAE of pancreatitis. No subjects experienced SAEs of hepatic failure, hepatitis, rash, Stevens Johnson syndrome, Toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, or aplastic anemia.

Below I summarize information for select SAEs of interest in the pooled safety population.

Encephalopathy
Three Fampridine SR subjects had SAEs of encephalopathy (subjects ACD-001246, ACD-001235, and ACD-000202). The encephalopathy SAE for subject ACD-001235 occurred approximately 15 days after stopping Fampridine SR (for seizure) and the event was attributed to baclofen. The encephalopathy event for subject ACD-000202 occurred after this subject mistakenly took up to 300mg of baclofen and then suddenly stopped. The event was attributed to baclofen withdrawal and the subject continued to take Fampridine SR in the trial. The event for subject ACD-001246 was not well described in the submitted narrative. This subject, a 55 year old female who received Fampridine SR for approximately 1 month (titrated to 30mg bid) experienced encephalopathy with associated hypokalemia and possible seizure. The patient, who had a history of episodes of dizziness worsening with migraines, had abruptly withdrawn from chronic use of clonazepam and Prozac® on the day of the event and was in a confused state. She experienced “tremulousness” without rhythmic jerking on the way to the emergency room and was treated with lorazepam and potassium replacement, after which she made a full recovery. The patient was discontinued from the trial (her last dose of Fampridine SR was on the day of the event). An EEG found no focal or epileptiform activity.

Anemia
Three Fampridine SR subjects had SAEs of anemia. Subject ACD-000085 was a 57 year old female who was hospitalized for anemia after one week of Fampridine SR treatment in this extension trial. In the previous controlled trial where this subject received Fampridine SR, her hemoglobin results were 12.3g/dL (screen), 11.7 g/dL (day 56), and 11.2 g/dL (day 119). This subject had screening tests for the extension trial and her hemoglobin was 7.2 g/dL (hematocrit 26.6%, no indices reported). She enrolled in the extension and 1 week later she had a hemoglobin of 5.9g.dL (hematocrit 20.6%) and was hospitalized and transfused 2 units of packed red blood cells. This event was presumed due to an upper GI bleed. The subject complained of upper GI pain that resolved with Tums, and admitted to frequent NSAID use and had been treated with steroids. She was treated with iron supplements and the event resolved. Subject ACD000162, a 50 year old female with a history of spinal cord injury and ulcerative colitis had an SAE of anemia that was attributed to her ulcerative colitis. Subject ACD-000403 was a 61 year old male with a spinal cord injury who complained of anorexia and nausea during treatment with Fampridine SR. The investigator noted that the subject’s hemoglobin decreased from 14.1 g/dL at baseline to 12.7g/dL (hematocrit decreased from 45.8% to 36.5%). The subject’s lab results included a normal haptoglobin and bilirubin and normal reticulocyte count. The subject had a normal ferritin, normal total iron binding

capacity, a decreased serum iron result and a decreased iron saturation, which are consistent with anemia of chronic disease. He denied vomiting, hematemesis, and bright red blood per rectum. The subject discontinued from the trial. The events resolved with omeprazole treatment.

Pancytopenia
Subject ACD-000628 had an SAE of pancytopenia. This subject was a 45 year old male with a spinal cord injury (T11-12). His baseline WBC count was 7.48 k/mm3, hemoglobin was 14.4 g/dL and platelet count was 202 k/mm3. After 2 months of Fampridine SR, the subject was seen for his last visit (trial closed by sponsor) and was found to have a WBC count of 3.45 k/mm3 (normal 3.5-10.5k/mm3) and a hemoglobin of 12.8g/dL (nl 13-17.5g/dL) and a platelet count of 193 k/mm3 (nl 140-370 k/mm3). The subject reported experiencing a GI illness with diarrhea just prior to these lab results. Fampridine SR was stopped and the subject was reported as having pancytopenia. Repeat labs 7 days later included a WBC count of 6.18 k/mm3, a hemoglobin of 14g/dL and a platelet count of 245k/mm3.

Pancreatitis
Subject ACD-000451 from trial 0296-003US was a 47 year old male with MS who was taking no other medications at the time he was diagnosed with pancreatitis. This subject presented with acute abdominal pain and was diagnosed with acute pancreatitis secondary to cholelithiaisis. He underwent a laproscopic cholecystectomy. Acorda reported that the event resolved and that the subject discontinued from the trial.

SAEs in MS Subjects, Controlled and Uncontrolled Trials
In Table 11 (Summary of Clinical Safety, pp. 38-9) Acorda noted that 19.3% (177/917) of Fampridine SR MS trial subjects experienced one or more SAEs. The SAEs experienced by more than 3 MS subjects were multiple sclerosis relapse (4.1%, n=38), convulsion (1.4%, n=13), urinary tract infection (1.4%, n=13), cellulitis (1.2%, n=11), pneumonia (1.1%, n=10), and sepsis (0.8%, n=7). Three MS subjects experienced SAEs of complex partial seizures (0.3%).

SAEs in the Adequate and Well Controlled MS trials
Table 10 (Summary of Clinical Safety, p.35) summarized SAEs by treatment for the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204). SAEs were 3 times more frequent among Fampridine SR subjects (6.5%, 33/507) compared to placebo subjects (2.1%, 5/238) in these trials and the risk for all SAEs among Fampridine SR subjects appeared dose related. Multiple sclerosis relapse was the only SAE that occurred in more than 2 Fampridine SR subjects (fampridine n=7, 1.4%; placebo n=0).

SAEs in SCI Subjects, Controlled and Uncontrolled Trials
In SCI trials, 8.6% (51/593) of subjects experienced one or more SAEs. The SAEs reported by more than 3 SCI subjects were convulsion (1%, n=6), cellulitis (0.8%, n=5), and urinary tract infection (0.8%, n=5) (ISS, Table 87, pp.205).

SAEs in the Non-patient population (Healthy volunteers, renal deficiency)
One patient (0.3%, 1/382) from the non-patient population reported an SAE (visual hallucinations) (ISS, p.205).

SAEs in Non-pooled Trials
Two subjects from trials excluded from the integrated safety analysis experienced SAEs. Following 5 doses of 4-aminopyridine (12.5 mg q 6 hours), a female MS patient from a clinical pharmacology trial (1091-001US) experienced what was described as a tonic-clonic seizure lasting 30 seconds with loss of consciousness lasting 1 minute. Plasma levels in the hospital at an unknown time interval following the event were 104ng/mL. The trial report provided no additional details about this event. In a Guillain-Barre syndrome trial, a 77 year old male subject experienced 2 days of tachycardia (not further specified) after approximately 3 weeks of 4- aminopyridine treatment. The subject was hospitalized and the tachycardia resolved without treatment. The subject continued treatment with 4- aminopyridine throughout the event and completed the trial.

SAEs in the Safety Update
Acorda reported that 17 Fampridine SR patients experienced 28 SAEs during the period covered by the Safety Update. The newly reported SAEs were Multiple sclerosis relapse (n=3), syncope (n=2), intracranial hemorrhage (n=1), pyrexia (n=1), dehydration (n=1), renal mass (n=1), urinary tract infection (n=1), pulmonary embolism (n=1), fall (n=1), appendicitis perforated (n=1), post-operative wound infection (n=1), adenocarcinoma (n=1), depressed level of consciousness (n=1), septic shock (n=1), Escherichia infection (n=1), pancreatitis (n=1), cholelithiasis (n=1), peripheral vascular disorder (n=1), chest discomfort (n=1), myocardial infarction (n=1), abdominal pain upper (n=1), nausea (n=1), vomiting (n=1), bile duct stenosis (n=1), and suicide attempt (n=1). No new seizure SAEs were reported in the Safety Update.

7.3.3 Dropouts and/or Discontinuations

In the Fampridine SR MS clinical trial population, AE and withdrawal of consent were the most common reasons for discontinuing from a Fampridine SR clinical trial. The following table summarizes the reasons for discontinuation from MS Fampridine SR trials in the NDA database.

Reasons for Discontinuation from MS Fampridine SR trials in the NDA database.

Patient Accounting	Total Fampridine MS	Adequate and Well Controlled MS Trials		Open Label MS trials>1 week
		Fampridine	Placebo	
Total exposed	1029	507	238	693
Completed	296 (29%)	475 (94%)	230 (97%)	24 (3%)
Ongoing	480 (47%)	0	0	484 (70%)
Discontinued	253 (25%)	32 (6%)	8 (3%)	185 (27%)
AE*	112	21	5	61
Non compliance	9	3	1	5
Withdrew consent	77	5	0	70
Lost to f/u	9	1	2	6
Other	49	2	0	44

*Includes both TEAEs and non TEAEs leading to discontinuation (Acorda submission dated 8/14/09).
From ISS Tables 17, 17.2.1, and 17.2.2

TEAEs Leading to Discontinuation, MS and SCI Trials, Pooled
ISS table 27.1.1 reported that 221 (14.6%, 221/1510) Fampridine SR MS and SCI subjects experienced one or more TEAEs leading to discontinuation. The System Organ Class (SOC) groupings with the most TEAEs leading to discontinuation were Nervous system disorders (8.5%, 128/1510), Psychiatric disorders (4.2%, 63/1510), General disorders and administration site conditions (3.4%, 52/1510), Gastrointestinal disorders (2.5%, 38/1510), and Musculoskeletal and connective tissue disorders (1.9%, 28/1510). No other SOC grouping of TEAEs leading to discontinuation included >1% of subjects. In the table below, I identify those specific TEAEs leading to discontinuation that were reported for at least 3 subjects in MS and SCI trials.

Treatment Emergent Adverse Events Leading to Discontinuation of at Least 3 Fampridine SR subjects in MS and SCI Trials

AE Preferred Term	N (%)	AE Preferred Term	N (%)
Dizziness	38 (2.5%)	Vomiting	4 (0.3%)
Insomnia	22 (1.5%)	Chest discomfort	4 (0.3%)
Convulsion	19 (1.3%)	Muscular weakness	4 (0.3%)
Asthenia	19 (1.3%)	Burning sensation	4 (0.3%)
Nausea	17 (1.1%)	Hypoaesthesia	4 (0.3%)
Anxiety	17 (1.1%)	Memory impairment	4 (0.3%)
Paresthesia	15 (1.0%)	Multiple sclerosis relapse	4 (0.3%)
Headache	14 (0.9%)	Abnormal dreams	4 (0.3%)
Muscle spasticity	12 (0.8%)	Disorientation	4 (0.3%)
Tremor	12 (0.8%)	Dyspnea	4 (0.3%)
Muscle spasms	10 (0.7%)	Anorexia	3 (0.2%)

Difficulty in walking	9 (0.6%)	Back pain	3 (0.2%)
Fatigue	9 (0.6%)	Hypertonia	3 (0.2%)
Confusional state	9 (0.6%)	Vertigo	3 (0.2%)
Vision blurred	7 (0.5%)	Abdominal pain upper	3 (0.2%)
Urinary tract infection	6 (0.4%)	Irritability	3 (0.2%)
Constipation	6 (0.4%)	Pneumonia	3 (0.2%)
Pain in extremity	6 (0.4%)	Neuralgia	3 (0.2%)
Gait disturbance	5 (0.3%)	Sensory disturbance	3 (0.2%)
Disturbance in attention	5 (0.3%)	Urinary incontinence	3 (0.2%)
Trigeminal Neuralgia	5 (0.3%)	Depression	3 (0.2%)
Hyperhydrosis	5 (0.3%)		

Source: ISS Table 27.1.1

In addition to the TEAEs leading to discontinuation above, the following TEAEs led to discontinuation of one subject each: pancreatitis (described above with SAEs), hypersensitivity, rash macular, skin exfoliation, and toxic skin eruption. No subjects discontinued for hepatic failure, hepatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, pancytopenia, or aplastic anemia.

Below I summarize information for select TEAEs leading to discontinuation for the pooled safety population.

Macular Rash
Subject MS-F202 EXT 19012, a 48 year old male discontinued from the trial for an AE of macular rash. After approximately 13 months of treatment with Fampridine SR in study MS-F202EXT, this subject developed a macular rash on his forehead. The narrative stated that approximately 8 months later he was treated with topical hydrocortisone. Apparently the rash persisted despite treatment for 3 months and he discontinued from the trial. The investigator rated the rash as mild in intensity.

Hypersensitivity
Subject SCI-F301 01702, a 33 year old male, discontinued from the trial for an AE of hypersensitivity. The narrative provided little useful information about this event, noting only that the subject experienced rib pain and “increased hypersensitivity” that was rated as moderate by the investigator. The event was reported as resolved on a follow up visit.

Skin exfoliation, Toxic skin eruption
Subject SCI-F301 03415, a 69 year old male, discontinued from the trial for an AE of skin exfoliation and toxic skin eruption. This subject started treated with Fampridine SR on 6/30/03. Fampridine was held for one dose on 7/17/03 for

elective urinary bladder surgery. On 8/25/03, the subject developed "toxic erythema" of the hands and trunk. On 8/27/03 he developed peeling skin on the hands. Fampridine SR was stopped and the subject was treated with corticosteroids. The event was resolved on 9/1/03.

TEAEs Leading to Discontinuation of MS Trial Subjects, Controlled and Uncontrolled Trials

ISS Table 27.2.1 listed TEAEs leading to discontinuation of Fampridine SR MS subjects from controlled and uncontrolled trials in the safety database. Eleven percent (102/917) of MS subjects had one or more TEAEs leading to discontinuation. The TEAEs leading to discontinuation of more than 3 MS subjects were convulsion (1.4%, n=13), balance disorder (0.9%, n=8), dizziness (0.8%, n=7), asthenia (0.7%, n=6), paresthesia (0.5%, n=5), trigeminal neuralgia (0.5%, n=5), headache (0.5%, n=5), confusional state (0.5%, n=5), multiple sclerosis relapse (0.4%, n=4), fatigue (0.4%, n=4), nausea (0.4%, n=4), and anxiety (0.4%, n=4). Three Fampridine SR MS subjects discontinued for TEAEs of complex partial seizures (0.3%).

TEAEs Leading to Discontinuation from Adequate and Well Controlled MS Trials

ISS Table 27.2.2 summarized AEs leading to discontinuation by treatment for the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204). In these trials, 3.4% (17/507) of Fampridine SR subjects had one or more TEAEs leading to discontinuation compared to 2.1% (5/238) of placebo subjects. The TEAEs leading to discontinuation of at least 2 Fampridine SR subjects and that led to discontinuation more frequently compared to placebo were headache (Fampridine SR 0.8%, 4/507; placebo 0/238), balance disorder (Fampridine SR 0.6%, 3/507; placebo 0/238), dizziness (Fampridine SR 0.6%, 3/507; placebo 0/238), and confusional state (Fampridine SR 0.4%, 2/507; placebo 0/238). One Fampridine SR (0.2%) and no placebo subjects discontinued for convulsion and no subjects discontinued for complex partial seizures.

TEAEs Leading to Discontinuation of SCI Subjects, Controlled and Uncontrolled Trials

In SCI trials, 20.1% (119/593) of Fampridine SR subjects had one or more TEAEs that led to discontinuation. The TEAEs leading to discontinuation of more than 3 SCI subjects were dizziness (5.1%, n=32), insomnia (3.4%, n=20), nausea (2.2%, n=13), asthenia (2.2%, n=13), anxiety (2.2%, n=13), muscle spasticity (1.9%, n=11), paresthesia (1.7%, n=10), tremor (1.7%, n=10), muscle spasms (1.5%, n=9), headache (1.5%, n=9), difficult walking (1.2%, n=7), balance disorder (1.2%, n=7), vision blurred (1%, n=6), fatigue (0.8%, n=5), urinary tract infection (0.8%, n=5), constipation (0.8%, n=5), vomiting (0.7%, n=4), convulsion (1%, n=6), pain in extremity (0.8%, n=5), disturbance in attention (0.8%, n=5), hyperhidrosis (0.8%, n=5), burning sensation (0.7%, n=4), muscular weakness (0.7%, n=4), memory impairment (0.7%, n=4), abnormal dreams (0.7%, n=4), confusional state (0.7%, n=4) (ISS, Table 27.3.1).

TEAEs Leading to Discontinuation for the Non-patient Population (Healthy volunteers, renal deficiency)
Four Fampridine SR subjects (1%, 4/382) had one or more TEAEs that led to discontinuation from the non-patient population. The TEAEs that led to discontinuation of at least 3 subjects were dizziness (0.8%, 3/382), and tremor (0.8%, 3/382) (ISS Table 27.4).

AEs Leading to Discontinuation in the Non-pooled Trials
Four subjects experienced AEs leading to discontinuation from trials excluded from the pooled safety analysis. A Guillain-Barre syndrome patient discontinued from trial CGBS Phase 2A for a "chronic demyelinating polyneuropathy". Three Guillain-Barre syndrome patients discontinued from trial CGBS Phase 2B for tremor, cramping, weakness, dizziness, ataxia, and diabetic hypoglycemia; weakness, tremors, and postural hypotension; and dizziness

TEAEs leading to Discontinuation in the Safety Update
Acorda identified 4 Fampridine SR subjects who discontinued from ongoing MS open-label extension trials for TEAEs during the period covered by the Safety Update. The events leading to discontinuation were myocardial infarction, depressed level of consciousness, intracranial hemorrhage (also reported as a death), and trigeminal neuralgia.

7.3.4 Significant Adverse Events

Seizures
Acorda explained that fampridine causes seizures, that this finding is consistent with the known pharmacology and toxicology of fampridine, and that the risk of seizure increases with fampridine C_{max} (Summary of Clinical Safety, p.39). One reason that Acorda gave for developing the Fampridine SR formulation was to reduce peak plasma levels associated with a given dose, presumably to reduce seizure risk. Acorda considered the seizure risk when designing Fampridine SR MS clinical trials. Potential study subjects were excluded if they reported a history of seizure, and MS study subjects with epileptiform activity on a screening EEG were excluded from clinical trials.

Acorda's presentations of seizure risk are based on the limited duration controlled trial data (9-15 weeks) and the longer duration, but uncontrolled, extension trial data. Acorda focuses their presentation on seizure risk in MS subjects exposed to the recommended Fampridine SR dose, 10mg bid, and also considers seizure risk in MS subjects exposed to higher Fampridine SR doses, MS subjects exposed to other fampridine formulations, and in SCI subjects (most of the SCI subjects were exposed to doses >10mg bid).

Seizure Risk in the General Population

Acorda cited an estimate of seizure prevalence in the general population of 0.5-1.0%. In addition, they cited annual epilepsy incidence estimates in the general population of 50/100,000 (Summary of Clinical Safety, p.41).

Seizure risk in MS patients
Despite evidence of an association between MS and seizure, precise, consistent quantitative risk estimates of this relationship are not available. Most of the available information about seizure risk among MS patients consists of prevalence estimates derived from cohorts. In a review of over 30 publications, Koch et al reported a range of seizure prevalence estimates in MS patients between 2-4%. Many of these publications did not distinguish between seizures that predated MS and those that arose after symptoms or diagnosis of MS.

Four publications reported epilepsy or seizure incidence or included incident cases of seizure and person time follow up data. Olafsson et al reported their experience in Iceland where 3 patients developed epilepsy (recurrent, 2 or more, unprovoked seizures >24 hours apart) after diagnosis of MS and one after developing symptoms of MS (but prior to MS diagnosis) during 2,771 person years of observation. These data yield an epilepsy incidence in MS patients of 140/100,000 PY (3-fold higher than their general population estimate). Nicoletti et al reported their experience from Catania, Italy where the age adjusted mean annual incidence of epilepsy (recurrent, 2 or more, unprovoked seizures >24 hours apart) among MS patients was 148/100,000 (4 cases among 170 MS patients). Eriksson et al reported their experience in Sweden where they found a yearly incidence of first seizure without identified cause among a cohort of 225 patients with probable or possible MS of 349/100,000. The authors also found that seizure incidence was increased among patients with progressive MS compared to those with relapsing remitting MS. Nyquist et al reported their experience in Olmstead County, MN where the incidence of seizure without identified cause after diagnosis of MS was 61/100,000 PY. The incidence of seizure without identified cause after development of symptoms of MS but prior to diagnosis was 80/100,000 PY. Interestingly, unprovoked seizure incidence in MS patients in this study was not different than the study's general population background unprovoked seizure incidence (61/100,000PY).

Preclinical data
Acorda explained that fampridine is a broad spectrum potassium channel blocker in the millimolar range of concentration and the plasma concentration with clinical use is <1 micromolar. At the plasma concentration achieved with clinical use, Acorda claims that fampridine is selective only for sensitive channels (i.e., in injured and demyelinated nerve fibers) (Summary of Clinical Safety, p.43).

In-vitro studies
Acorda reported that in-vitro brain slice experiments showed amygdala and hippocampus epileptiform discharges when perfused with solutions of fampridine at concentrations of 5 to 500 μM.

Animal studies
Acorda noted that a 2-week repeated dose study in rats found seizures at a dose of 10mg/kg/day given as a single oral dose but not at 3mg/kg/day or less. Acorda also reported that a fampridine dose of 12mg/kg/day was well tolerated when divided into 4 doses throughout the day (supporting seizure risk is related to Cmax rather than AUC).

In dogs exposed to fampridine, Acorda reported that a 2-week oral toxicity study resulted in seizures and death in 3 of 4 dogs assigned to a single 3mg/kg dose. In a 1-year repeated dose toxicity study in beagles, seizures were observed in those given 1.5 or 3mg/kg/day in 2 divided doses (mean plasma concentrations 117-287 and 130-399 ng/mL) but not in those given 0.75 mg/kg/day (plasma conc. 64.7-160 ng/mL).

Human data

MS Clinical Pharmacology Trials
Acorda reported that no seizures were observed in MS subjects in clinical pharmacology trials.

MS Clinical Trials
As previously noted, Acorda considered seizures occurring during clinical trials as events of special interest. In order to minimize the number of MS study subjects at increased risk of seizures from being exposed to Fampridine SR, Acorda excluded patients with a history of seizure and screened patients with EEGs prior to enrollment in MS randomized controlled trials. Furthermore, after completing a randomized controlled trial and prior to entering an open label extension, all MS subjects were again screened with EEGs. Acorda reported that subjects were excluded if they had “evidence of epileptiform activity” on screening EEG. Acorda did not provide in their protocols specific EEG criteria defining “evidence of epileptiform activity” and admitted that individual study sites excluded patients for a variety of EEG findings. Acorda did not analyze the specific EEG criteria used by study sites to exclude subjects (Response to reviewer questions dated 5/20/09).

In response to reviewer inquiry, Acorda provided two tables summarizing the numbers of study subjects excluded from Fampridine SR MS clinical trials for EEG findings. The following table identifies the number of subjects excluded from randomized controlled trials.

Number of Screened Subjects Excluded for EEG Abnormalities, MS Randomized Controlled Trials

	Study				
	MS-F201	MS-F202	MS-F203	MS-F204	Total
Number Screened	42	271	401	362	1076

Number (%) excluded	1 (2.4%)	11 (4.1%)	10 (2.5%)	15 (4.1%)	37 (3.4%)

Source Acorda submission dated 5/20/09

The following table summarizes the number of subjects excluded from open label extension trials, stratified by treatment in the preceding randomized controlled trial.

Number of Screened Subjects Excluded for EEG Abnormalities, MS Extension Trials Overall and Stratified by Treatment in Preceding RCT

	Study Pair			Total
	MS-F202 MS-F202 EXT	MS-F203 MS-F203 EXT	MS-F204 MS-F204 EXT	
Number Screened	153	271	219	885
Number (%) excluded	4 (2.6%)	2 (0.7%)	5 (2.3%)	11 (1.2%)
Number (%) excluded that received fampridine in RCT	3/122 (2.5%)	0/202	1/108 (0.9%)*	5/432 (1.2%)
Number (%) excluded that received placebo in RCT	1/31 (3.2%)	2/69 (2.9%)	3/111 (2.7%)	6/211 (2.8%)

*An additional patient from this study initially had an abnormal screening EEG, was subsequently re-screened and had a normal EEG and then was allowed to continue in the extension study.

None of the 12 patients from MS-F201 screened for the MS-F202EXT study were excluded for EEG screen abnormalities.

Randomized, Placebo-Controlled MS trials
Acorda pooled data from the following RCTs in MS patients: MS-F201, MS-F202, MS-F203, and MS-F204 (note this is different from prior analyses that presented data for adequate and well controlled trials and that did not include MS-F201). In these 4 trials, 532 subjects were randomized to fampridine and 249 to placebo. Five seizure AEs (0.9%) were observed in fampridine subjects and 1 (0.4%) in a placebo subject.

When Acorda presented risks by dose for these trials they included all subjects exposed to each dose so that subjects titrated to higher doses appear in more than one dose category. These trials had the following dose groups 10mg bid, 15mg bid, 20mg bid, 25mg bid, 30mg bid, 35mg bid, and 40mg bid. For the 10 mg bid dose group, Acorda included all subjects (N=532) in the denominator since all subjects were exposed to this dose (subjects randomized to higher doses were titrated through this dose on the way to their target dose, even though they received this dose briefly). The risk by dose that I present below use the number randomized to the dose as the denominator.

Given that trial MS-F201 was so differently designed than the other three randomized placebo controlled trials (MS-F201 included fewer subjects, and titrated subjects to higher fampridine doses) it is preferable to consider the results for MS-F201 separately. In MS-F201, 25 subjects were randomized to fampridine and 11 to placebo. The fampridine subjects started at 10mg bid and the fampridine dose was increased in weekly intervals to a target dose of 40mg bid. In this study, no placebo and 2 fampridine (8%) subjects experienced seizures. The fampridine subjects were receiving 30mg bid and 35 mg bid doses at the time of the seizures. I provide clinical details from the submitted information about these seizures in the following paragraphs.

30mg bid
Subject #03002 from study MS-F201, a 55 woman with primary progressive MS (EDSS=3.5), experienced an episode of encephalopathy and a possible tonic seizure, which was observed by paramedics. The narrative reported that the subject experienced “tremulousness” without rhythmic jerking. An EEG found no focal or epileptiform activity. Three days before the event, at Study Visit 5, after a week of 25 mg b.i.d. treatment, her plasma fampridine concentration was 117.0 ng/mL. This case was complicated by the fact that the patient suddenly stopped taking clonazepam and began a new treatment with sumatriptan for migraine just prior to the event. The patient was experiencing hypokalemia and refractory migraine at the time. Other concomitant medications at the time of the event included Prozac and Excedrin.

35mg bid
Subject #02006 from study MS-F201, a 61 year old woman with secondary progressive MS (EDSS=6.5), experienced a period of confusion, apnea, and possible seizure at a dose of 35 mg b.i.d. and was hospitalized for two days. In previous weeks of treatment, the patient’s plasma fampridine concentrations had been 44.4 ng/mL at 15 mg b.i.d., 61.6 ng/mL at 20 mg b.i.d., and 99.6 ng/mL at 25 mg b.i.d. At visit 6, three days prior to the event, and following a week of treatment at the 30 mg b.i.d. dose, the plasma concentration was below the limit of quantitation (<2ng/mL). This same patient experienced an episode of encephalopathy and possible seizure that was considered secondary to baclofen treatment 17 days after discontinuation of Fampridine SR. Other concomitant medications included estrogen, progesterone, amitriptyline, fosamax, and Fleets suppository.

The 3 adequate and well controlled trials were similarly designed, included treatment durations of 9-15 weeks, and exposed most Fampridine SR subjects to doses of 10 mg bid (Study MS-F202 exposed 50 subjects to 15mg bid and 57 subjects to 20mg bid).

The following table summarizes the seizure risk data for the 3 adequate and well controlled MS trials MS-F202, MS-F203, and MS-F204.

Seizure Risk Data for MS Trials MS-F202, MS-F203, and MS-F204

Study	Placebo	Total Fampridine	Fampridine 10mg BID	Fampridine 15mg BID	Fampridine 20mg BID
MS-F202	(0/47)	1.3% (2/159)	(0/52)	(0/50)	3.5% (2/57)
MS-F203	(0/72)	0.4% (1/228)	0.4% (1/228)	-	-
MS-F204	0.8% (1/119)	(0/120)	(0/120)	-	-
Total	0.4% (1/238)	0.6% (3/507)	0.3% (1/400)	(0/50)	3.5% (2/57)
	1.6/100 PY (1/62PY)	2.1/100 PY (3/142PY)	0.9/100 PY (1/108PY)	- (0/16 PY)	11.8/100 PY (2/17PY)

These pooled data demonstrate an increased seizure risk for all Fampridine SR subjects compared to placebo subjects. When risk is stratified by Fampridine SR dose, there is evidence of an increased seizure risk at 20mg bid, based on a small number of events and limited exposure.

I provide clinical details from the submitted information describing the seizures. Division neurologists Drs. Dunn and Illoh reviewed all available information about these events. They agreed that the events reported for the Fampridine SR subjects were likely seizures. They disagreed about whether the event reported for the placebo subject represented a seizure.

10mg bid
Subject #14003 from study MS-F203 was a 58 year old woman with secondary progressive MS (EDSS=6) assigned to 10 mg bid Fampridine SR. After 61 days on double blind treatment she experienced a severe case of sepsis, secondary to community acquired pneumonia. In the emergency room she experienced an apparent focal seizure, involving shaking of an extremity. It is not known when the patient may have taken the last dose of Fampridine SR prior to this event. Concomitant medications at the time of the event included oxybutinin, Prozac, oxycodone, calcium, Fosamax, Avonex, Tylenol, and Bactrim DS.

20mg bid
Subject #04006 from study MS-F202, was a 58 year old man with primary progressive MS (EDSS=6). He had been taking Fampridine SR for 33 days when he experienced a generalized seizure while riding on a bus, approximately 7.5 hours after taking his last dose of 20 mg Fampridine SR. He was taken to the emergency room and observed to have tongue lacerations. A CT scan was unremarkable. He was treated with methylprednisolone, fospheytoin, and Dilantin and was discharged the following day. Five days earlier, at Study Visit 4, his plasma concentration of fampridine at approximately 6 hours post dose had been 35.5 ng/mL. Concomitant medications at the time of the event were baclofen and Viagra.

Subject #07019 from study MS-F202, a 47 year old woman with secondary progressive MS (EDSS=4), experienced a partial complex seizure after taking a double dose of 20 mg Fampridine SR (total 40 mg) to compensate for a previously missed dose. She was found by her father who reported that she was unresponsive with automatisms, and later was confused, tremulous, and diaphoretic. She did not recall the event and did not seek medical treatment. On the day of the overdose (Study Visit 7, 49 days on double blind treatment) the patient's plasma fampridine concentration at approximately 4.5 hours post dose was 79.0 ng/mL and she experienced a partial complex seizure of moderate severity 4 hours later. With reassurances of future compliance, the patient was allowed to continue in the trial but, ten days later, she again took two doses within a short period of time. She became confused for about an hour and was discontinued from the study at that point. An EEG performed 1 week later showed "bilaterally independent mild temporal slowing with some rare sharp waves, more prominent on the left than on the right, indicative of a tendency for partial seizures." Concomitant medications included Betaseron and Lexapro.

Placebo
Subject #028/408 from study MS-F204, a 65 year old female with secondary progressive MS, hypercholesterolemia, hypertriglyceridemia, osteopenia, osteoarthritis, and breast cancer, experienced an AE coded as complex partial seizures. After approximately 58 days on placebo the patient "watched an entire movie, and upon completion was not able to recall the title or details of the movie." The investigator felt that the patient possibly had a complex partial seizure. On the subsequent 2 days, the patient lost her balance and fell, with no significant injuries noted. Other symptoms noted around this time were increased parasthesis in the hands, increased fatigue, difficulty with short term memory, and worsening gait imbalance. An EEG performed 5 days after the event showed no evidence of epileptiform activity but did show mild intermittent bitemporal slowing more prominent on the left side. Her screening EEG showed mild intermittent left temporal slowing. Six days after the event the patient reported that her paresthesias, balance, and memory were improving. She had no further amnestic episodes. On follow up, 17 days after the event, the patient reported increased leg weakness, leg paresthesias, and increased paresthesias in her hands and was diagnosed with an MS exacerbation and treated with IV methylprednisolone.

Open label MS trials
In Table 13, Acorda reported seizure risk observed during MS open label trials. I summarize data from that table below.

Seizure Incidence and Dose at Time of Occurrence in Open-Label Extension Trials of Fampridine SR in MS through July 31, 2008

	MS-F202EXT >10mgbid*	MS-F202EXT 10mgbid	MS-F203EXT 10mgbid	MS-F204EXT 10mgbid	Total 10mgbid
Subjects exposed	175	177	269	214	660
Patient years	115	422	513	125	1060
Subjects with seizure AE	2	1	4 [1,2]	0	5
%	1.14%	0.56%	1.5%	0	0.76%
Incidence per 100 PY (95% CI)	1.7 (0.21-6.28)	0.24 (0.01-1.32)	0.78 (0.21-2.00)	0	0.47 (0.15-1.10)

*Using the exposure datasets, I determined that the person time exposure in 202EXT at >10mg bid is almost entirely to 15mg bid, with <2PY exposure to 20mg bid.
1 One of these cases was a patient taking a very high dose of Detrol-LA (tolterodine) 12 mg b.i.d. at the time of the seizure. She discontinued from both fampridine and Detrol and experienced another seizure one year later, on resuming Detrol treatment.
2 One additional patient (#23015) experience seizure at 22 days following discontinuation from Study MS-F203EXT due to an MS relapse. This patient was not included here as the event is not likely associated with fampridine, given the length of time off treatment, the rapid clearance of fampridine, and the lack of any known association between withdrawal and seizure. The event was evaluated by the investigator as unlikely related to treatment.
bid = Twice daily; CI = Confidence interval; EXT = Extension; MS = Multiple sclerosis; SR = Sustained release.

Two of the open label trial subjects included above received placebo in their preceding RCTs (2/205) and the remainder received fampridine in the preceding RCT.

I summarize the seizure events in the following paragraphs.

10mg bid
Subject #25016, a 60 year old female who received Fampridine SR in a preceding controlled trial, started open label Fampridine SR in study MS-F203EXT on 4/25/06. On (b) (6), she started tolterodine (8mg then 12 mg 12 hours later). Other concomitant medications were Diovan, Aricept, and Estradiol. On (b) (6), the subjects husband observed her, body rigid and convulsing, for approximately 3 minutes. The event occurred approximately 9 hours after her last dose of Fampridine SR. She was observed in an emergency department and Fampridine SR and tolterodine were stopped. The subject restarted tolterodine in (b) (6) and on (b) (6) experienced a grand mal seizure lasting approximately 10 seconds. Concomitant medications included Aricept and Diovan.

Subject #16001, a 46 year old female who received Fampridine SR in a preceding controlled trial, started open label Fampridine SR 10mg bid on 3/27/06. On (b) (6) the subject's daughter found her in the bathroom shaking, and the subject had vomited. EMTs witnessed the subject's seizure and administered valium 5mg iv which had no effect. In the ED, the subject was

observed to be unresponsive with eyes deviated to the left. The patient was able to move all 4 extremities, but was not able to follow commands. The subject had an initial glucose of 147 (no units) and SBP was in the 80's (increased to 114 with iv fluids). The subject was intubated and administered propofol. A head CT showed normal ventricles, no evidence of intra or extra axial mass, and no sign of an acute stroke or hemorrhage. She was started on Dilantin and fine tremors were noted. Propofol was increased. Seizure activity continued and additional Dilantin and Ativan were administered. The patient was given antibiotics and underwent an LP which showed clear, colorless CSF, glucose 74, protein 52, WBC count 2/mm3 and 0 RBCs. Urine toxicology was negative for PCP, cocaine, amphetamines, cannabinoids, opiates, barbiturates, and methadone and positive for benzodiazpines. The subject was transferred to another hospital and was observed to be seizing despite continued propofol and Ativan. The patient was treated with Phenobarbital, the propofol infusion was increased and the Ativan infusion was continued. A repeat CT was negative and an EEG showed a burst suppression pattern that was invariant throughout the tracing. No evidence of electrographic status was seen. The bursts were not associated with visible musculoskeletal accompaniment (half of the EEG was performed with video). The subject was admitted to the ICU and her course was complicated by development of a left pneumothorax requiring chest tube placement. Repeat EEG documented "…some degree of healthy variability. In the initial part of the recording EEG features of a moderate encephalopathic 'process age encountered'. However, today the latter half of the recording architectural features of normal non-REM sleep were emerging which would appear to designate a moderate but potentially reversible encephalopathic process due to the preservation and emergence of such normal sleep architecture. Evidence of ongoing status epilepticus or even a seizure tendency is not noted in this recording". The patient required additional chest tubes and subsequently underwent a tracheostomy. The subject's mental status improved and she was transferred to a general care floor. A PEG was placed (aspiration shown on swallowing studies). The subject was discharged on (b) (6) with tracheostomy and PEG tube. Concomitant medications included Betaseron and baclofen.

Subject #35002, a 64 year old male who received Fampridine SR in a preceding controlled trial, started open label Fampridine SR 10mg bid on 4/26/06. On (b) (6) the subject reported visual disturbances and noted that he was leaning to one side. He called for his wife and when she arrived she witnessed him shaking and unconscious. He was taken to an ER and was told that he had a seizure. He had been unconscious for approximately 45 minutes. The report for an EEG performed on (b) (6) noted "…excessive fast activity, which may be related to medication effect; however, no suspect medications were listed for this patient. Further, the appearance of right temporal rhythmic theta and right temporal sharp waves are suspicious for a right temporal epileptogenic brain abnormality; however, because these waveforms occasionally have an appearance of

wickets, which is a normal variant, we recommend repeating a study with sleep deprivation." A sleep deprived EEG was reportedly normal. The subject discontinued from the trial. Concomitant medications included Maxide, Lisinopril, and Valium.

Subject #21009, a 62 year old female who received Fampridine SR in a preceding controlled trial started open label Fampridine SR 10mg bid on 1/24/06. On (b) (6), while at a rehabilitation facility, recovering from a fall, a physician witnessed the subject experience a 90 second episode of generalized rigidity and rhythmic shaking. She was unresponsive during and for 10-15 minutes following the episode. She was given iv Dilantin and transferred to an acute care hospital. She complained of blurry vision, tinnitus, and garbled speech. A brain MRI showed no acute intracranial abnormalities or evidence of acute intracranial hemorrhage or ischemia. The subject discontinued from the trial. The subject continued Dilantin until 5/14/08. Concomitant medications included tizanidine, baclofen, buspirone, interferon beta 1b, oxazepam, and propranolol.

Subject #22031, a 48 year old female who received Fampridine SR in a preceding controlled trial, started treatment with open label Fampridine SR 10mg bid on 7/6/04. She was titrated to 15mg bid on 7/14/04 and remained on that dose until 3/30/05 when she was down titrated to 10 mg bid. On (b) (6) she experienced an episode where her eyes rolled back, her arm stiffened, and she could not swallow or spit out saliva from her mouth. This event was diagnosed as a partial complex seizure. She did not experience tongue biting or incontinence. She was taken to an ER and an EEG and MRI were reportedly unremarkable. Subsequently, she was seen by a neurologist and started on Keppra. She also experienced an episode of "shaking of the trunk". The subject did not report these events to the study site until 8/16/07, at which time she was discontinued from the trial. The narrative noted that the subject reported 2 episodes of undiagnosed "convulsions" during sleep that occurred 1 and 2 years prior to this event. This subject was taking no other medications at the time of the event.

15mg bid
Subject #22024, a 59 year old female who received placebo in a preceding controlled trial, started open label Fampridine SR 10mg bid on 6/8/04. She was titrated up to a dose of 15mg bid on 6/14/04. On (b) (6) she experienced a seizure (not described) and was taken to an ER and admitted to a hospital. Her initial EEG showed mild, diffuse, encephalopathy with epileptic activity in the left hemisphere suggesting the possibility of a recent CVA. Repeat EEGs showed decline in epileptic potentials. MRI showed stable MS lesions and 2 foci of enhancement with volume loss in the left hemisphere. A repeat EEG approximately 6 weeks after the event showed no epileptiform abnormalities. The subject was initially treated with Dilantin and then switched to Keppra. She was discontinued from the trial and following discharge from the hospital was sent to

a rehabilitation facility. Concomitant medications were Reminyl, azathioprine, and baclofen.

Subject #22039, a 63 year old male who received placebo in a preceding controlled trial, started open label Fampridine SR 10mg bid on 8/5/04. He was titrated up to a dose of 15mg bid on 8/12/04. On (b) (6) he experienced a generalized motor seizure and was taken to an ER. He reported symptoms of gastroenteritis for a few days prior to the event. An EEG found mild to moderate diffuse encephalopathy. MRI was consistent with MS but did not show enhancing lesions. The subject was treated with carbamazepine and was sent home from the ER. He was discontinued from the study. Concomitant medications were lovastatin and baclofen.

Seizures in MS subjects exposed to other fampridine formulations
Six of 178 (3.3%) MS subjects exposed to other fampridine formulations experienced seizure AEs. All six events were classified as generalized seizures. One event occurred in a subject that had been treated for 22 months at a dose of 12.5mg bid (Subject #105, study 1293-001EXT). Three events occurred within the first 3 days of treatment, another at day 8 and another at day 26. The three cases with rapid onset of seizure occurred after relatively high doses of fampridine. In the first case (subject #107, Study 0293-001) the seizure occurred after two doses at 40 mg b.i.d. In the second case (patient #1091-001), the seizure occurred at two hours after the third dose of 12.5 mg q6h, and, in the third case, following two doses of 12.5 mg at 7 hours apart and an accidental overdose of 25 mg (2x12.5 mg) after another 9 hours (patient #210, Study 0494-001).
Plasma samples were obtained from these three patients in the hospital and showed plasma concentration of fampridine of 202 ng/mL, 104 ng/mL, and 114 ng/mL respectively. These concentrations were greater than the maximum plasma concentration expected with the 10 mg bid dose of Fampridine-SR. The two remaining cases also occurred in Study 0494-001. Patient #261 experienced a seizure 8 days after initiation of treatment at 12.5 mg bid at approximately 10 hours following the last dose. Patient #414 experienced a seizure after 26 days of treatment at a dose of 17.5 mg bid and approximately 7 hours post dose. No fampridine plasma concentration measurements were obtained in these cases.

SCI Clinical Pharmacology Trials
There were no seizures in SCI CP trials

Double Blind Controlled SCI Trials
One Fampridine SR (0.27%, 1/372) and no placebo subjects (0/324) experienced a seizure during double blind controlled Fampridine SR SCI trials. The seizure occurred in a subject exposed to 40mg bid (4.3%, 1/23). No seizures were reported for subjects exposed to 17.5 mg bid (n=29), 20mg bid (n=66), 25mg bid (n=245). The seizure event is summarized below.

Subject #02C04, was a 67 year old male, randomized to Fampridine SR 40 mg bid in study SCI-F201. This subject experienced a 10-15 minute tonic-clonic seizure followed by a post-ictal period of several hours. The seizure occurred approximately 7 hours following his last scheduled dose of 40 mg Fampridine SR, a dose he had been taking for one week. He was treated with phenytoin and carbamazepine. A head CT showed no evidence of new focal injury, stroke, or hemorrhage. Blood chemistry test results were unremarkable. An EEG showed no evidence of seizure activity or seizure focus. This patient had experienced dizziness and nausea for some days prior, had discontinued the use of tizanidine the day before, and experienced hallucination the same day as the seizure. Concomitant medications included Zanaflex, baclofen, and Coumadin.

Open Label SCI Trials
Acorda reported that 5 SCI subjects (1.4%, 5/354) experienced seizures during open label Fampridine SR trials. One subject experienced a seizure while taking 25mg bid and the remaining 4 subjects were taking 30mg bid, 35mg bid, and 40mg bid (n=2). The subjects had been taking Fampridine SR in the extension study for 1-13 months prior to these events. I summarize these events below.

25mg bid
Subject #05Y12, a 41 year old male, started open label Fampridine SR 10mg bid on 8/21/02, and was up titrated to 30mg bid on (b) (6). Approximately 5 1/2 hours after his first 30mg dose (b) (6) he experienced a seizure lasting 10 minutes which was associated with respiratory arrest that required rescue breathing. He was taken to an ER and a head CT and EEG were reportedly normal. The subject discontinued from the study. The narrative noted that this subject was also taking baclofen at the time of the event.

30mg bid
Subject #06B02, a 50 year old male, started open label Fampridine SR 10mg bid on 11/12/02, was up titrated to 40mg bid on 12/24/02 and then down titrated to 30mg bid on 9/8/03. On (b) (6), his wife found him in the driveway of his home and noted that he was conscious but combative and confused. This lasted for 10 minutes. EMS restrained him and transported him to an ER. He was calm on arrival at the ER but could not recall the prior events. He had normal results for an EEG, head CT, cardiac enzymes, CBC, BNP, and brain MRI/MRA. He was discharged home on (b) (6) and was discontinued from the trial. The narrative noted that this subject was also taking bupropion and baclofen at the time of the event.

35mg bid
Subject #03K06, a 46 year old female, started open label Fampridine SR 10mg bid on 6/25/02, was up titrated to 40mg bid and then down titrated to 35mg bid on 8/20/02. On (b) (6), she experienced a seizure lasting 10 minutes. She was

taken to an ER and experienced a second seizure lasting 10 minutes. She was treated with Ativan and Dilantin and admitted to the hospital. She had normal results for an EEG, thyroid profile, brain CT and brain MRI. She was discontinued from the trial and was treated for a UTI. The narrative noted that this subject was also taking baclofen at the time of the event.

40mg bid
Subject #12V10, a 53 year old female, started open label Fampridine SR 10mg bid on 8/26/03 and was titrated to 40mg bid on 11/18/03. On (b) (6), she had a seizure (not described). She was taken to an ER and treated with Ativan and Dilantin. She was discharged home on (b) (6) and continued on Dilantin. The narrative included no information about diagnostic workup for this event. The subject was discontinued from the trial. The narrative noted that this subject was also taking baclofen, diazepam, and gabapentin at the time of the event.

Subject #03W12, a 38 year old female, started open label Fampridine SR 10mg bid on 2/10/03 and was up titrated to 40mg bid on 3/24/03. On (b) (6), he experienced a seizure lasting 10 minutes. He was taken to an ER and experienced a second seizure lasting 5 minutes. An EEG, thyroid profile, and CT scan were reportedly normal. He was started on Keppra and was treated for a UTI. He was discontinued from the trial. The narrative noted that this subject was also taking baclofen and tizanadine at the time of the event.

Fampridine Plasma levels and Seizure risk
Acorda summarized available plasma level data collected during the development program. Acorda noted that study AN751-101 found a mean Cmax of 25.2ng/mL and an upper range of 44.7 ng/mL among 24 MS patients following a single 10mg dose. In the 2 pivotal trials, sparse sampling showed maximum mean plasma concentrations of 29.2 and 30.2 ng/mL. The highest recorded plasma fampridine concentrations in these 2 trials were 66.8 and 87.3 ng/mL. Among volunteer patients with severe renal deficiency, the mean Cmax following a single 10mg BID dose was 42.7ng/mL.

Among the 7 patients with seizures that also had fampridine plasma concentration data, the concentrations ranged from 104 to 475ng/mL. Acorda feels that this data supports that “a plasma fampridine concentration of approximately 100 ng/mL is likely to represent a threshold for increased risk of seizure in the absence of other significant risk factors.” (Summary of Clinical Safety, p.51). Acorda does concede that seizures have occurred in patients where plasma concentrations were likely in the normal therapeutic range and notes that it is not clear if fampridine contributed to the seizures in these cases or if there were other predisposing factors.

Acorda summarized seizure risk data from other medications approved in the US for the treatment of MS. Acorda presented data from package inserts, from publically available FDA clinical reviews, and from advisory committee briefing documents. Acorda

acknowledged 2 difficulties in using such data for comparisons to fampridine including the use of different inclusion exclusion criteria (ex. fampridine excluded MS patients with seizure history of epileptiform activity on EEG), and differences in study conduct (Acorda reported all seizures as SAEs).

Acorda noted that the incidence of convulsions in placebo treated subjects in Avonex, Betaseron, and Rebif trials ranged from 0 to 1.1/100PY while the incidence in the actively treated groups range from 0.2 to 2.7/100PY. In the Avonex pivotal trial, the incidence of seizures for Avonex was 1.4/100PY (n=4, 3 with no prior history of seizure) with no seizures in the placebo group. In the European Betaseron trial ME 93079 the incidence of seizure was 0.8/100 PY (n=8) for Betaseron and 0.6/100PY (n=6) for placebo. In the North American Betaseron trial in Secondary progressive MS the incidence of seizures for Betaseron was 0.4/100PY and for placebo was 0.2/100PY (only SAEs reported).

I read selected FDA clinical reviews for MS treatments and summarized findings with respect to seizure risk in the following table:

Drug	Review	Study size	Duration	Type	Risk
Rebif (IFN B-1a)	5/2/03	Rebif 339 Avonex 337	48 weeks	SAE	Rebif 0/339 Avonex 1/337
Rebif	2/9/99	PBO 187 Rebif 22 mcg 188 Rebif 44mcg 184	2 years	SAE	0 0 0
Avonex (IFN B-1a)	5/17/96	Avonex 158 PBO 143		AE	4/158 0/143
Avonex	5/23/03	Avonex (OL) 153	24 months	AE	Did not make >=2%

I also present labeling for these medications and summarize references to seizure risk below:

Avonex has the following Precautions statement in labeling:

> Caution should be exercised when administering AVONEX® to patients with pre-existing seizure disorders. In the two placebo-controlled studies in multiple sclerosis, 4 patients receiving AVONEX® experienced seizures, while no seizures occurred in the placebo group. Three of these 4 patients had no prior history of seizure (see ADVERSE REACTIONS). It is not known whether these events were related to the effects of multiple sclerosis alone, to AVONEX®, or to a combination of both. The effect of AVONEX® administration on the medical management of patients with seizure disorder is unknown.

Seizure risk is described for patients in the Avonex Medication Guide.

Rebif has the following Precautions statement in labeling:

> Caution should be exercised when administering Rebif to patients with pre-existing seizure disorders. Seizures have been associated with the use of beta interferons. A relationship between occurrence of seizures and the use of Rebif has not been established.

In the Rebif AE table that appears in labeling, seizure risk is summarized as follows: Convulsions PBO 2% (n=187), Rebif 22mcg 5% (n=189) Rebif 44mcg 4% (n=184)

The Medication Guide for Rebif does not mention seizure risk but instructs patients to tell their physician if they have epilepsy.

Copaxone does not have a Precautions statement in labeling for seizures. In premarketing studies (n=979) convulsion was reported as an infrequent AE (1/100-1/1000) for Copaxone. In Copaxone RCTs, seizure risk did not meet the criteria for inclusion in the AE table (>=2% and greater on Copaxone compared to placebo; Copaxone n= 563 PBO n= 564).

Betaseron does not include a Precaution statement for seizure in its label. Seizure did not meet criteria for the Betaseron RCT AE table (>=2% greater on Betaseron compared to placebo; Betaseron n=1115, PBO n=789). Convulsion is mentioned among post marketing events reported with Betaseron. The Betaseron Medication Guide does not mention seizure risk but instructs patients to tell their physician if they have epilepsy.

Discussion
Although there is no disagreement about the ability of fampridine to cause seizures, the relevant question is whether Fampridine SR increases seizure risk at the dose intended for the treatment of MS patients (10mg bid). Data from the controlled clinical trials at the 10mg bid dose did not suggest a difference in seizure risk compared to placebo but this comparison relies on only 400 Fampridine SR treated patients, 238 placebo patients and only 2 seizure events. In these same trials, at 20mg bid (only a doubling of the dose intended to be marketed), the seizure risk was 10-fold higher (based on 2 events in 57 subjects), a concerning finding suggesting a narrow therapeutic index. In the open label trials, the seizure risk in those treated with 10mg bid was similar to the risk seen in the Fampridine SR subjects treated with 10mg bid during controlled trials. The results from this open label population must be considered very carefully since this was a highly selected group of patients. These patients were screened by history and EEG prior to the RCT, those with exposure to Fampridine SR in the RCT (roughly 2/3 of open label trial participants) survived a trial of therapy without seizure, and then all subjects were screened with EEG again prior to entering the open label trial.

Comparing the seizure risk in the Fampridine SR clinical trial population with background data or data from other MS drug development programs must also be viewed with caution. The screening in the Fampridine SR trials and usual concerns about potentially important differences among the Fampridine SR population and the general MS background population or other drug development program populations make these comparisons problematic.

The current evidence suggests a dose-related risk of seizure with Fampridine SR, with limited data at the dose intended for treatment, and a suggestion of increasing risk just above therapeutic dose. If the risk benefit for Fampridine SR is favorable and the drug is approved, Fampridine SR should not be used in patients with seizure history and prospective patients should be screened with EEG prior to treatment, the conditions of use in the clinical trials. Fampridine SR labeling should include information about the potential for increased seizure risk at the intended dose, should strongly warn about not increasing the dose above the recommended dose and should urge caution in patients at risk for higher plasma exposures (ex. renal insufficiency). A Medication Guide should explain the risk for patients and include information about not increasing the dose.

Multiple Sclerosis Relapse

Acorda examined the risk for multiple sclerosis relapse among MS study subjects exposed to Fampridine SR. Acorda explained that relapses were initially coded to the COSTART term “aggravation reaction” and were to the MedDRA terms “multiple sclerosis” and “multiple sclerosis relapse” (Summary of Clinical Safety, p.54). Acorda also recognized the possibility that relapse events reported using the verbatim term “exacerbation” could be coded to the MedDRA term “condition aggravated” and found one subject where this was the case.

Results from the pooled analysis of AEs from the adequate and well controlled MS trials suggest an increased risk of multiple sclerosis relapse TEAEs among Fampridine SR subjects compared to placebo subjects and the risk among Fampridine SR subjects increased with increasing dose. The following table summarizes the MS relapse risk in the adequate and well controlled MS trials.

MS Relapse Risk in the Adequate and Well Controlled MS Trials

Event	Placebo (n=238)	Total Fampridine (n=507)	Fampridine 10mg bid (N=400)	Fampridine 15mg bid (n=50)	Fampridine 20mg bid (n=57)
MS Relapse	3.8% (n=9)	6.5% (n=33)	5.3% (n=21)	8% (n=4)	14% (n=8)
	14.5/100PY	23.1/100PY	19.2/100PY	24.9/100PY	46.4/100PY

From Table 22.2.2a

Given these results, Acorda examined when MS relapse AEs occurred during the study. In an analysis submitted on 5/28/09, Acorda provided the MS relapse risks and rates

from the RCTs MS-F202, MS-F203, and MS-F204 and separately for the open label extensions for these same trials. For the RCTs, Acorda classified the MS relapse AEs by the trial period (pre-treatment, double blind period, and post treatment follow up) that they occurred. I provide those results below.

MS Relapse Risks from RCTs by Trial Period and in Open Label Extensions

	Placebo Events/N (%)	Placebo Events/Patient years	Fampridine 10mg events/N (%)	Fampridine 10mg events/Patient years
RCTs MS-F202, MS-F203, and MS-F204				
Pre-treatment	0/238 (0)	0/100	6/400 (1.5%)	19.6/100
Double blind	8/238 (3.4%)	15.2/100	16/400 (4%)	17/100
Follow up	1/238 (0.4%)	11/100	6/400 (1.5%)	39.1/100
Open label extension trials MS-F202EXT, MS-F203, MS-F204				
	N/A	N/A	151/660 (22.8%)	14.2/100

According to table 22.2.2.b, in these RCTs, the MS relapse risk on active treatment for the 15mg bid group was 6% (3/50; 21.2/100PY) and for the 20mg bid group was 7% (4/57; 26.5/100PY).

This table suggests that the difference in MS relapse risk when comparing Fampridine SR and placebo in the RCT study data are driven by differences in the post treatment period, when subjects were not taking Fampridine SR. There appeared to be little difference in risk between Fampridine SR 10mg bid and placebo for the double blind periods of the RCTs. The MS relapse risk for the 15mg and 20mg bid groups was slightly higher, with a limited number of study subjects at these doses. The MS relapse risk during the open label trials was similar to the risk observed during the double blind period of the RCTs.

Acorda determined that a number of events occurred either during down titration (for those dosed above 10mg bid) or during the post treatment follow up period. After removing these cases from consideration, the MS relapse risks were as follows:

Study	Placebo	Total Fampridine	Fampridine 10mg BID	Fampridine 15mg BID	Fampridine 20mg BID
MS-F202	2.1% (1/47)	5.0% (8/159)	3.8% (2/52)	6% (3/50)	5.3% (3/57)
MS-F203	4.2% (3/72)	3.1% (7/228)	3.1% (7/228)	-	-
MS-F204	3.4% (4/119)	3.3% (4/120)	3.3% (4/120)	-	-
Total	3.4%	3.7%	3.3%	6.0%	5.3%

	(8/238)	(19/507)	(13/400)	(3/50)	(3/57)

Using the submitted AE data set I examined the cases of treatment emergent MS relapse in the adequate and well controlled MS trials. The commonly used verbatim terms for events coded to the MedDRA term “Multiple Sclerosis relapse” for Fampridine SR subjects were MS exacerbation (n=22), MS relapse or Relapse (n=7), MS worsening (n=2), MS exacerbation increased worsening tremors and increased leg weakness (n=1), unable to walk (MS exacerbation) (n=1), increased MS fatigue (n=1), worsening of MS symptoms (n=1) and MS relapse involving sensory system (n=1). For the placebo subjects, the verbatim terms coded to Multiple Sclerosis relapse were MS exacerbation (n=4), MS relapse (n=3), MS worsening (n=1), and Worsening of MS symptoms (n=1).

In the RCTs, of the 33 Fampridine SR subjects (36 events) with MS relapse, 6 had SAEs compared to none of the 9 placebo subjects. Of the 6 serious AEs in Fampridine SR subjects, 4 occurred during treatment and 2 after treatment completed (2 days and 4 days). Using investigator severity assessments, for Fampridine SR treated subjects 3 relapses were considered mild, 27 moderate, and 6 severe. For placebo relapses, 4 were mild and 4 were moderate.

Acorda felt the data did not indicate an increased risk of MS relapse with ongoing treatment. Acorda felt the overall incidence of MS relapse in their trials (14/100PY) was low. They also note that “There was a higher frequency of events categorized as MS relapse following discontinuation of treatment, some of which may derive from worsening of MS with respect to the on-treatment neurological condition.”

Given that the available data did not allow the Division to determine the nature of these events, it was not possible at this time to determine if these “relapses” represented a waning drug effect or new neurological deficits that would suggest actual relapse events as suggested by the AE terms. The Division asked the sponsor to return to study sites in order to collect additional information about the nature of these events.

In response to the Division’s request to better characterize AEs coded to the preferred term “MS relapse”, Acorda undertook additional exploratory efforts. In a submission dated 8/12/09, Acorda explained that they identified all events that could reasonably have been coded to “MS relapse”; reconstructed the clinical details of these events to the extent possible using Adverse Event pages, notations in Clinical and Subject Global Impression comments fields, Subject Summary Questionnaires, etc.; and made queries to investigational sites with respect to events in the post-treatment period, including requests for clarification from source documents regarding any additional verbatim descriptions of events. Acorda also collected and analyzed additional information on the occurrence of pre-treatment MS relapse events to the extent that it was available (MS-F203 and MS-F204 only).

Based on this re-characterization of events, Acorda presented the following tables summarizing risks for MS relapse by treatment in the MS adequate and well controlled trials:

Table 1. Events of "Multiple Sclerosis Relapse" in the Adequate and Well-Controlled Studies MS-F202, MS-F203 and MS-F204 Fampridine-SR 10 mg b.i.d. vs. placebo in MS-F202, MS-F203 and MS-F204

	Pre-treatment	During Treatment	Post-Treatment	Treatment Emergent	Uncontrolled Studies
Fampridine-SR 10 mg b.i.d.					
N	400	400	400	400	660
Approx. Patient-Years	23.1#	94.1*	15.4#	109.5	1213.2
Pts with MS Relapse	7	15	7	21	165
% Pts with MS Relapse	1.75%	3.75%	1.75%	5.25%	25%
Patients/100 pt-yrs	30.3	15.9	45.5	19.2	13.6
Events of MS-Relapse	7	15	7	22	250
Events/100 pt-yrs	30.3	15.9	45.5	20.1	20.6
Placebo					
N	238	238	238	238	
Approx. Patient-Years	13.7#	52.6*	9.2#	61.8#	
Pts with MS Relapse	1	9	1	9	
% Pts with MS Relapse	0.42%	3.78%	0.42%	3.78%	
Patients/100 pt-yrs	7.3	17.1	10.9	14.6	
Events of MS-Relapse	1	9	1	10	
Events/100 pt-yrs	7.3	17.1	10.9	16.2	

Pt-years calculated from ISS Table 22.2.2b

 # Estimate of Pt-years from number of patients enrolled and duration of period per protocol

Fampridine-SR 15 and 20 mg b.i.d in MS-F202 and MS-F202 EXT

	Pre-treatment	During Treatment	Post-Treatment	Treatment Emergent	Uncontrolled Studies +
Fampridine-SR 15 mg b.i.d.					
N		50	50	50	175
#Approx. Patient-Years		13.5	2.9	16.4	108.1@
Pts with MS Relapse		3	2	4	15
% Pts with MS Relapse		6%	4%	8%	8.6%
Patients/100 pt-yrs		22.2	69.3	24.5	13.9
Events of MS-Relapse		3	2	4	17
Events/100 pt-yrs		22.2	69.3	24.5	15.7

Fampridine-SR 20 mg b.i.d.					
N		57	57	57	10
[#]Approx. Patient-Years		15.3	3.3	18.6	1.54[@]
Pts with MS Relapse		3	5	8	0
% Pts with MS Relapse		5.3%	8.8%	14%	0%
Patients/100 pt-yrs		19.5	152.1	42.9	0
Events of MS-Relapse		5	5	10	0
Events/100 pt-yrs		32.6	152.1	53.7	0

[#] Estimate of Pt-years from number of patients enrolled and duration of period per protocol
[+] Extension data from MS-F202EXT Study Report, Table 10
[@] Exposure data from Table 7.0 page 6 in ISS

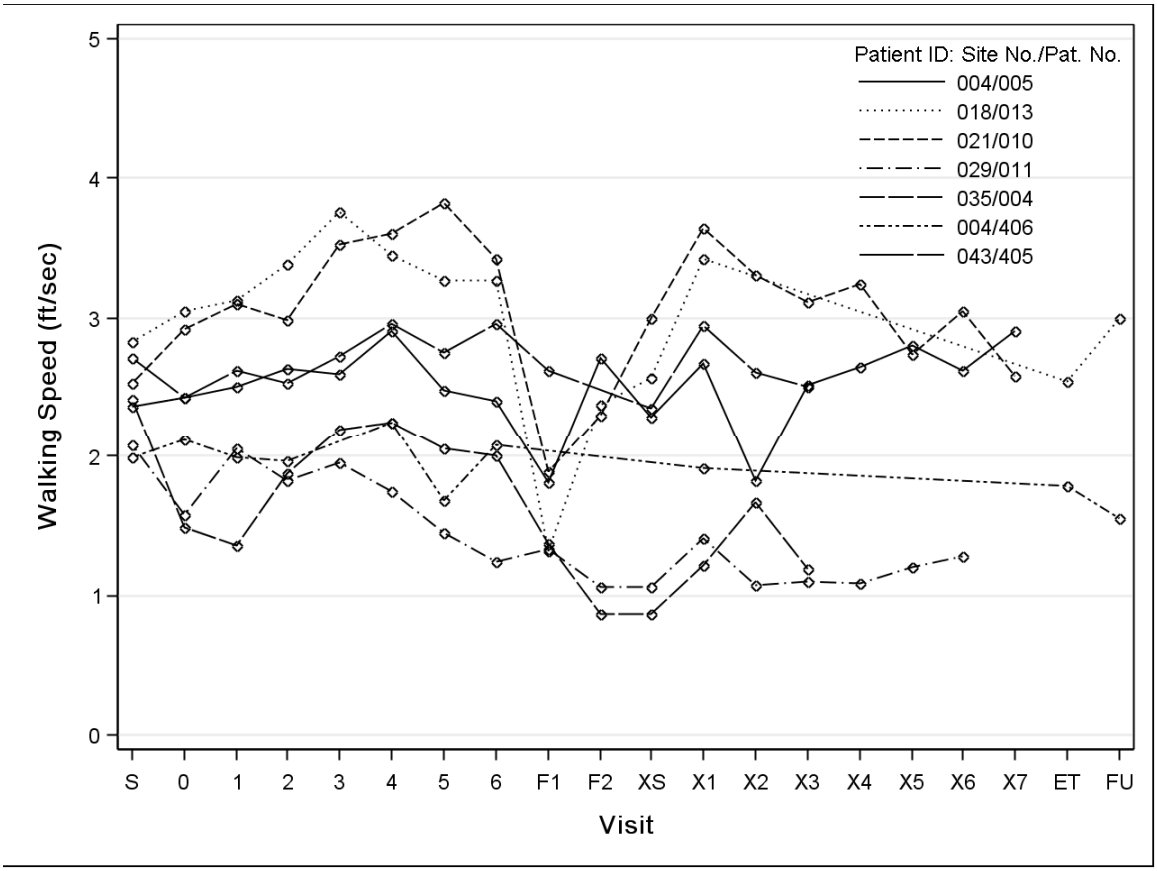
Acorda notes that the incidence of MS relapse during double blind treatment is similar for Fampridine SR and placebo for all three of the studied doses (when using patients with an event/100PY) and that the incidence during double blind treatment is similar to the incidence seen during open label extension trials. Acorda also notes that there is an increased risk for MS relapse events in the post treatment period that is dose related.

Acorda feels that these post-treatment events are due to "dose-related discontinuation effects that are transient and occur during the down-titration and post-treatment periods in a small proportion of patients."

Acorda also commented that the short observation periods for pre-treatment and post-treatment demonstrated a higher incidence of relapse in the fampridine groups and a lower incidence in the placebo group when compared to the longer double blind period and that this finding reflects the "difficulty in estimating event rates from such short observation periods."

Acorda reported that for the 7 Fampridine 10mg bid subjects that experienced post treatment MS relapse AEs, all 7 events occurred within 1-6 days after stopping treatment, that none of these events were SAEs and that all 7 subjects enrolled in open label extension trials (5 still participating) and only 1 of the 7 experienced another relapse during the extension trial.

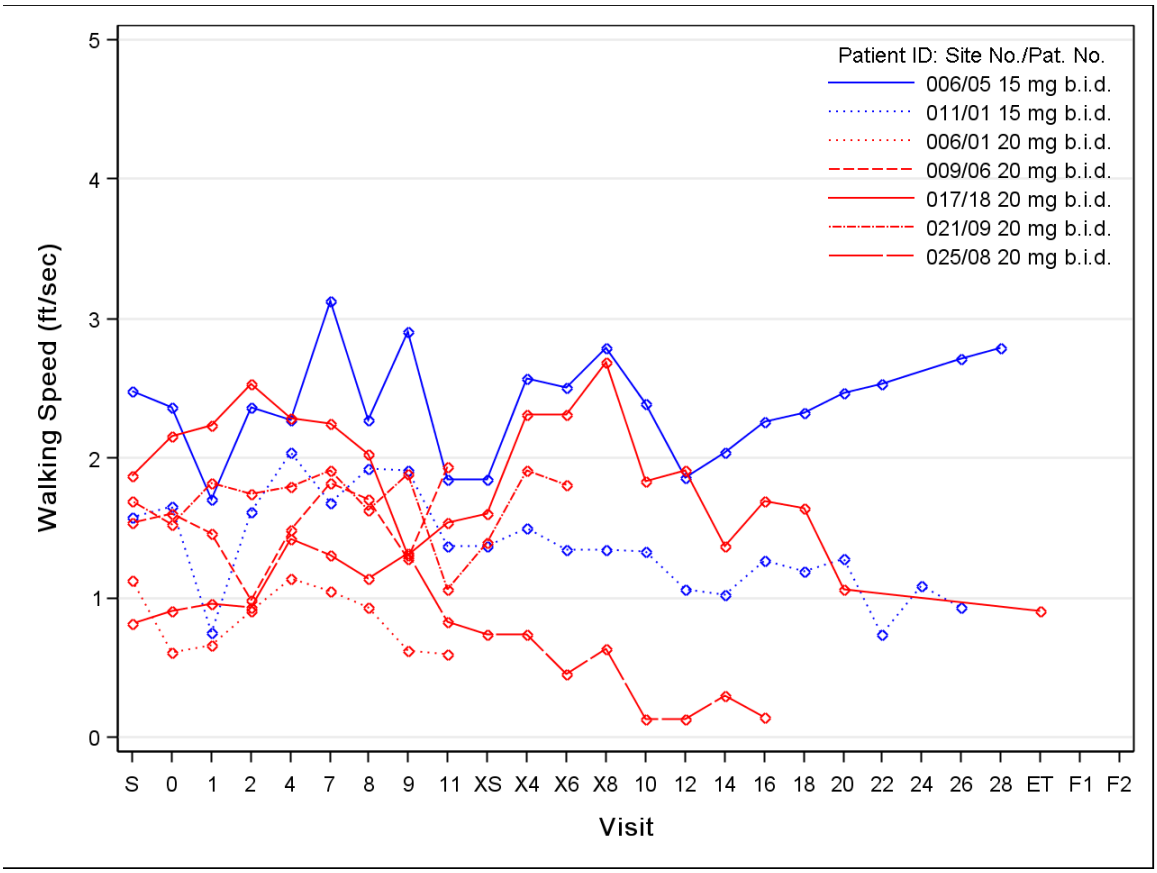
Acorda provided the following graph of walking speed for the 7 Fampridine SR 10mg bid patients with post treatment MS relapse AEs, where F1 and F2 are the post-treatment visits and Xn are the open label extension visits.



Acorda felt that the plots of walking times indicated that most patients experienced transient declines in walking speed after stopping treatment. Although not mentioned by Acorda, one might also appreciate that, after initial improvements in walking speed, the declines for most of these patients actually began at or prior to visit 5, during active treatment, but that the declines became more pronounced after stopping treatment.

Of the 7 Fampridine SR patients at doses above 10mg bid with MS relapses after discontinuation of treatment (2-15mg bid, 5-20mg bid) 3 events occurred during down titration and 4 events occurred after stopping active treatment (1-8 days). Two of these post treatment MS relapse events were SAEs. Five of the 7 patients that experienced post treatment MS relapse AEs continued Fampridine SR treatment in extension trials (4 still active, three have had additional MS relapse events).

Acorda provided the walking speed data for the Fampridine SR 15mg bid and 20mg bid patients that experienced post treatment MS relapse AEs. I provide that plot below.



In this graph, the follow up visit was visit 11 and Acorda noted that the interval between visit 11 and the screening visit for the extension study (XS) was approximately 9 months.

Acorda felt that these data support that these patients at 15mg bid and 20mg bid "experienced a decline in walking speed in the post-treatment period that could be observed at the two week follow up visit."

Acorda examined the available clinical data regarding the MS relapse AEs and concluded that "There were no clear differences between events of MS relapse occurring in the post treatment period and those occurring at other times in the study." Acorda admits that the verbatim terms for these events were not helpful.

Acorda compared demographic data for MS relapse patients and found no factors that distinguished subjects with post treatment MS relapse from the rest of the study population.

Acorda concludes that Fampridine SR treated patients and physicians should anticipate the possibility of worsening MS symptoms after discontinuing treatment. Acorda feels that this deterioration represents loss of therapeutic effect and that it is unlikely that

these events represent “true MS relapse in the sense of new or heightened inflammatory activity in the CNS.” Acorda points to the number of patients with post treatment MS relapse that continued into extension trials, many without additional MS relapse, as a reassuring factor.

FDA Review
Dr. Jody Green, a Division neurologist, reviewed the clinical data presented in the narratives that Acorda submitted for patients with MS relapse. Dr. Green felt that the narratives lacked objective description of signs that were present in these patients. Dr. Green was not able to determine whether these events represented MS relapse or decline in status following cessation of a drug that had been effective in these patients.

Discussion
As Acorda explained, in the adequate and well controlled MS trials, there was a dose dependent increased risk for MS relapse AEs in Fampridine SR subjects. The increased risk occurred during the post treatment phase of these trials. The post treatment phase was short in duration (only 2 weeks) meaning that this finding is based on very limited observation time. Looking at the placebo subjects, where one might not expect variability in risk by study phase, MS relapse risk was 7.3/100PY in the pre-treatment phase, 17.1/100 PY during the double blind phase, and 10.9/100PY during the post treatment phase. Also complicating this assessment is the suggestion of differences between the placebo and Fampridine SR groups based on the pre-treatment, baseline data. The MS relapse risk in the Fampridine SR group prior to initiating treatment was 4-fold higher (30.3/100PY) than the risk in the placebo group during the pre-treatment phase (7.3/100PY).

The reason for the observed difference in MS relapse risk between Fampridine SR subjects and placebo subjects is not clear. Acorda’s explanation, that the MS relapse AEs represent a waning therapeutic effect following discontinuation seems to be a reasonable explanation. Unfortunately the available data presented in the narratives for these events are not sufficient to allow differentiation between waning therapeutic effect and relapse of the MS disease process. In fact, in some cases, these events appeared to be true relapses to clinicians because the events resulted in hospitalization and treatment with steroids. Given the inherent complexity in diagnosing MS relapse, this finding might be expected.

The data from patients who experienced relapse during the post treatment phase and who continued in open label extension phases is reassuring. These data did not suggest continued uniform increased MS relapse risk among these patients. Furthermore, there did not appear to be increased MS relapse risk in the extension trial patients compared to the RCT patients.

Acorda suggests that patients and physicians should be counseled to expect the possibility of worsening MS symptoms after discontinuing treatment. Acorda did not

suggest how this might be accomplished. Labeling language and discussion in the Medication Guide could accomplish this goal.

Psychiatric AEs
When examining AE risks by Body system classification, Acorda noted an increased risk of Psychiatric AEs among Fampridine SR treated subjects compared to placebo subjects in the MS adequate and well controlled trials. This difference in risk was driven primarily by increases in risk among Fampridine SR subjects for anxiety and insomnia.

In the adequate and well controlled MS trials, the risk for anxiety among placebo subjects was 0.4% (1/238) compared to 1.8% (7/400) for Fampridine SR 10mg bid, 2% (1/50) for Fampridine SR 15mg bid, and 3.5% (2/57) for Fampridine SR 20mg bid. One anxiety event (Fampridine SR) was an SAE in these trials and one anxiety AE (Fampridine SR) led to discontinuation. The finding of increased risk of anxiety AEs with Fampridine SR was replicated in the SCI adequate and well controlled trials. The anxiety risk for SCI patients receiving placebo was 1.3% (3/229) compared to 4.9% (12/247) for SCI patients receiving Fampridine SR 25mg bid and 30% (9/30) for SCI patients receiving Fampridine SR 40mg bid (ISS table 22.3.2a). In SCI adequate and well controlled trials one anxiety event was an SAE (Fampridine SR 25mg bid). In the SCI adequate and well controlled trials, one placebo patient (0.4%, 1/229) discontinued for anxiety compared to 2 Fampridine SR 25 mg bid patients (0.8%, 2/247) and 1 Fampridine SR 40mg bid patient (3.3%, 1/30).

In the adequate and well controlled MS trials, the risk for insomnia among placebo subjects was 3.8% (9/238) compared to 9.3% (37/400) for Fampridine SR 10mg bid, 18% (9/50) for Fampridine SR 15mg bid, and 12.3% (7/57) for Fampridine SR 20mg bid. None of these insomnia AEs were classified as SAEs and no subjects discontinued from these trials for insomnia. The finding of increased risk of insomnia AEs with Fampridine SR was replicated in the SCI adequate and well controlled trials. The insomnia risk for SCI patients receiving placebo was 4.8% (11/229) compared to 10.9% (27/247) for SCI patients receiving Fampridine SR 25mg bid and 33.3% (10/30) for SCI patients receiving Fampridine SR 40mg bid (ISS table 22.3.2a). In SCI adequate and well controlled trials no insomnia events were SAEs, and one placebo patient (0.4%, 1/229) discontinued for insomnia compared to 6 Fampridine SR 25 mg bid patients (2.4%, 6/247) and 2 Fampridine SR 40mg bid patient (6.7%, 2/30).

Acorda noted that there was no evidence of an increased risk of depression with Fampridine SR based on AE data from active treatment periods. During active treatment, there did not appear to be differences in the risk for depression when comparing Fampridine SR to placebo, but when examining all TEAEs (on drug and up to 2 weeks following discontinuation) the depression risk for placebo was 0.8% (2/238) compared to 1.3% (5/400) for Fampridine SR 10mg bid, 2% (1/50) for Fampridine SR 15mg bid, and 3.5% (2/57) for Fampridine SR 20mg bid. Four of the Fampridine SR depression AEs (1-10mgbid, 1-15mg bid, and 2-20mg bid subjects) occurred during the

14-day follow up period, after discontinuation of Fampridine SR. None of the depression AEs were SAEs or led to discontinuation from the adequate and well controlled MS trials. In the SCI adequate and well controlled trials, the risk for depression AEs was 3.1% (7/229) for placebo patients compared to 4.9% (12/247) for Fampridine SR 25mg bid patients and 0 (0/30) for Fampridine SR 40mg bid patients. Unlike the MS controlled trials, all of the depression AEs in SCI trials occurred during active treatment. While none of the depression AEs from the adequate and well controlled SCI trials were SAEs, 3 depression AEs led to discontinuation (all 3 Fampridine SR 25mg bid).

In addition to depression AEs, the NDA integrated safety database included one subject who committed suicide (MS-203 EXT 220011, described above with the deaths), one subject who attempted suicide (MS-F203 EXT, 34008) and three subjects who had AEs of suicidal ideation (MS-F203 EXT15001 SAE, SCI-F201 05T02, SCI-F201 EXT 05M11). The subject who attempted suicide (MS-F203 EXT, 34008) was a 46 year old female with a history of MS and depression. One month after being diagnosed with renal carcinoma she attempted suicide by ingesting 250 acetaminophen tablets and an unspecified number of aspirin tablets and Tylenol #3 tablets. She survived the event and discontinued from the study. The subject who had a suicidal ideation SAE (MS-F203 EXT15001) was a 50 year old female with a history of MS, depression, and suicidal ideation, who developed suicidal ideation requiring psychiatric evaluation. Contributing stressors included worsening MS, marital discord, family changes, and social isolation. Her citalopram dose was increased and she discontinued from the study.

In their Safety Update, Acorda reported 2 events of suicide attempt and 2 events of suicidal ideation. The first report of suicide attempt was an update of the event described above for subject MS-F203 EXT 34008 (update included the stop date for the event). The second report described a 56 year old male with MS, hypertension, elevated triglycerides, pulmonary embolism, UTI, and anxiety. He was taking multiple medications including bupropion, escitalopram and seroquel. He ingested alcohol and medications (not specified) in a suicide attempt. He survived this attempt and continued in the study. This subject subsequently committed suicide (slashed wrists and stabbed self in the abdomen) but this event was not included in the above list of deaths because it occurred after the Safety Update database lock date.

The 2 subjects with suicidal ideation AEs (MS-F203 EXT 19006, 35004) both had histories of depression that predated study participation and both continued in the study. Neither event was an SAE.

The clinical trial data support a causal relationship between anxiety and insomnia and Fampridine SR. These events occurred more frequently in Fampridine SR subjects than in placebo subjects and the risk appeared dose related. There was insufficient evidence to establish a relationship between Fampridine SR and depression AEs.

Urinary Tract Infections
Acorda noted that urinary tract infection (UTI) AEs occurred commonly in the Fampridine SR NDA. The risk of UTI AEs among Fampridine SR subjects in controlled trials (both MS and SCI) exceeded the risk among placebo subjects. In MS adequate and well controlled trials, when considering AEs coded to the preferred terms UTI, cystitis, kidney infection, bacterial pyelonephritis, and Echerichia UTI, the risk among Fampridine SR subjects was 16.2% (82/507) compared to 10% (24/238) for placebo subjects. In SCI adequate and well controlled trials, the risk for those same AEs plus UTI enterococcal and urosepsis among Fampridine SR subjects was 28.9% (80/277) compared to 18.8% (43/229) for placebo subjects. Acorda noted that in the majority of cases, UTI AEs were diagnosed based on symptoms and that there was a lack of objective data (urinalysis results, urine culture results) supporting these diagnoses. Routinely collected UA data from adequate and well controlled MS trials showed that 25.1% (126/502) Fampridine SR subjects had leucocytes on UA compared to 30.9% (73/236) of placebo subjects. In SCI trials, 41% (83/202) of Fampridine SR subjects had positive leukocyte esterase results compared to 42% (78/187) of placebo subjects.

Despite the increased risk for UTI AEs among Fampridine SR subjects in adequate and well controlled trials, there were few UTIs that were SAEs and less consistent findings regarding difference in risk for UTI SAEs by treatment. In MS controlled trials, 4 Fampridine SR subjects experienced a UTI SAE (0.8%, pyelonephritis n=1, kidney infection n=1, and UTI n=2) compared to 1 (0.4%, UTI) placebo subject. In SCI trials, the risk for UTI SAEs was 0.7% for fampridine (2/277, UTI n=2) and 2.2% for placebo (5/229, UTI n=3, pyelonephritis n=1, urosepsis n=1).

Acorda postulated that Fampridine SR, which is excreted by the kidney and reaches high urinary concentrations, may produce sensory symptoms that are similar to the symptoms of UTI. They offered no empirical evidence to support this theory. In fact, when examining AEs from the Renal and Urinary Disorders body system grouping from the adequate and well controlled MS trials, except for urinary frequency (coded to pollakiuria) and urinary incontinence there is little evidence of a disparity of urinary symptoms when comparing fampridine subjects to placebo subjects. I provide that information in the following table.

Treatment Emergent Renal and Urinary Disorder AEs from Adequate and Well Controlled MS trials

	Placebo (n=238)	All Fampridine (n=507)	Fampridine 10mg bid (n=400)	Fampridine 15mg bid (n=50)	Fampridine 20mg bid (n=57)
Renal and Urinary Disorders	5.9% (14)	7.3% (37)	6.8% (27)	6% (3)	12.3% (7)
Bladder discomfort	0.4% (1)	0	0	0	0
Bladder spasm	0	0.2% (1)	0.3% (1)	0	0
Dysuria	0.4% (1)	0.4% (2)	0.5% (2)	0	0
Hematuria	1.7% (4)	0.2% (1)	0.3% (1)	0	0
Leukocyturia	0.4% (1)	0.2% (1)	0.3% (1)	0	0

Micturition urgency	1.7% (4)	1% (5)	1% (4)	2% (1)	0
Nephrolithiasis	0	0.6% (3)	0.8% (3)	0	0
Nocturia	0.4% (1)	0.2% (1)	0.3% (1)	0	0
Pollakiuria	0.8% (2)	2.4% (12)	2% (8)	2% (1)	5.3% (3)
Polyuria	0	0.2% (1)	0.3 (1)	0	0
Pyuria	0	0.2% (1)	0.3% (1)	0	0
Renal disorder	0.4% (1)	0	0	0	0
Terminal dribbling	0	0.2% (1)	0.3% (1)	0	0
Urinary hesitation	0	0.2% (1)	0.3% (1)	0	0
Urinary incontinence	0	1.6% (8)	1.3% (5)	0	5.3% (3)
Urinary retention	0.4% (1)	0.6% (3)	0.3% (1)	2% (1)	1.8% (1)
Urine odor abnormal	0	0.4% (2)	0	0	3.5% (2)

Data From Table 22.2.2a

Similar findings were seen in the adequate and well controlled SCI trials (data not presented).

The AE data from the Fampridine SR clinical trials (both MS and SCI) suggested an increased risk for urinary tract infections in Fampridine SR patients compared to placebo patients. In many cases, these events were diagnosed based only on symptoms and UA and/or urine cultures were not performed. There did not appear to be consistent increases in risk among Fampridine SR subjects compared to placebo subjects for serious UTIs (elevated in MS patients but not in SCI patients). There is insufficient evidence to evaluate Acorda's hypothesis that these UTI events represent sensory symptoms rather than actual infections. Any future planned Fampridine SR trials should attempt to clarify the association between Fampridine and UTI, perhaps by questioning all study patients about urinary symptoms and collecting cultures and UAs in symptomatic patients.

Hepatic Injury Report

Although there were no reports of hepatic injury in the Fampridine SR NDA or Safety Update, and no signal for hepatic injury from lab data (see below), a published article described a case of hepatic injury in a patient treated with 4-aminopyridine.[1] The authors described a 60 year old female who developed malaise after 6 months of treatment with 4-aminopyridine (30mg in three daily doses) and 6 weeks after a course of intravenous steroids for MS. The patient was found to be slightly jaundiced and testing found a bilirubin of 33 umol/L, (1.9mg/dL), GGT 199 U/L, AST 359 U/L, and ALT 819 U/L (ALP not reported). These abnormalities were not present immediately following treatment with steroids. 4-aminopyridine was stopped. The report noted that the patient had negative results on serological tests (not specified). The patient's condition improved over the subsequent 3 months with no additional interventions.

[1] Polman CH, Bertelsmann FW, van Loenen AC, Koetsier JC. 4-Aminopyridine in the Treatment of Patients with Multiple Sclerosis. Arch Neurol. 1994;51:292-296.

The limited information provided about this case of hepatic injury does not allow for definitive determination about the role of 4-aminiopyridine in this event. The transaminase data suggest hepatocyte injury in this patient, but the limited lab data does not allow one to determine if the patient's bilirubin exceeded 2.0mg/dL at any point. The summary of this case does not allow one to determine if other causes of liver injury were excluded. The authors did not describe which serologies were performed, if other testing was performed, or if the patient was taking any other medications. Given the lack of a signal for hepatic injury in the Fampridine SR NDA, and the lack of additional similar cases in the medical literature, it is premature to conclude that Fampridine SR causes hepatic injury. Acorda should closely follow and promptly report any liver injury cases reported for Fampridine SR.

7.3.5 Submission Specific Primary Safety Concerns

No additional submission specific primary safety concerns were identified during this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

AEs in MS and SCI Trials, Pooled
Acorda reported that 93.8% (1417/1510) of MS and SCI trial subjects exposed to Fampridine SR experienced one or more TEAEs (ISS Table 20.1.1). In the following table, I list the treatment emergent AEs that occurred in at least 2% of Fampridine SR subjects.

Treatment Emergent AEs ≥2% of Fampridine SR Subjects, MS and SCI Trials

AE Preferred Term	**% (n)**	**AE Preferred Term**	**% (n)**
Urinary tract infection	28.9% (436)	Excoriation	4.2% (63)
Dizziness	19.7% (298)	Pyrexia	4.1% (62)
Insomnia	19% (287)	Dyspepsia	4% (61)
Fall	18.1% (274)	Sinusitis	4% (60)
Headache	17.9% (270)	Influenza	3.9% (59)
Asthenia	15.5% (234)	Shoulder pain	3.9% (59)
Nausea	15.3% (231)	Pollakiuria*	3.6% (55)
Fatigue	13.2% (199)	Pharyngolarygeal pain	3.2% (48)
Paresthesia	13% (196)	Stomach discomfort	3.1% (47)
Multiple sclerosis relapse	12.9% (195)	Micturition urgency	3.1% (47)
Muscle spasms	12.2% (184)	Cystitis	3% (46)

Upper resp tract inf	12% (181)	Myalgia	3% (45)
Muscle spasticity	11.3% (171)	Neck pain	2.9% (44)
Constipation	11% (166)	Skin laceration	2.9% (44)
Back pain	10.6% (160)	Hyperhidrosis	2.9% (44)
Pain in extremity	10.5% (159)	Decreased appetite	2.7% (41)
Arthralgia	9.4% (142)	Cough	2.7% (41)
Diarrhea	9% (136)	Gastroenteritis viral	2.6% (40)
Edema peripheral	8.5% (128)	Vision blurred	2.6% (39)
Nasopharyngitis	7.7% (117)	Abdominal pain upper	2.5% (38)
Contusion	7.2% (108)	Abdominal pain	2.5% (38)
Balance disorder	7% (106)	Muscle tightness	2.5% (37)
Anxiety	6.5% (98)	Dyspnea	2.5% (37)
Hypoaesthesia	6% (90)	Erythema	2.4% (36)
Depression	6% (90)	Cellulitis	2.3% (35)
Musculoskeletal stiffness	5.4% (81)	Joint swelling	2.3% (35)
Tremor	5.4% (81)	Vertigo	2.3% (34)
Urinary incontinence	5.1% (77)	Fecal incontinence	2.3% (34)
Vomiting	4.8% (73)	Bronchitis	2.2% (33)
Pain	4.4% (67)	Hypertension	2.2% (33)
Rash	4.4% (67)	Abnormal dreams	2.2% (33)
Burning sensation	4.4% (66)	Gait disturbance	2.1% (32)
Difficulty walking	4.3% (65)		

From ISS Table 22.1.1a
*Urinary frequency

AEs in MS Subjects, Controlled and Uncontrolled Trials
The frequency of AEs in the MS trials (94.1%) was similar to the frequency observed for the pooled MS and SCI trials. The table below lists the AEs that occurred in at least 2% of MS subjects. This table is includes many of the same AEs listed in the preceding table. The following AEs occurred in at least 2% of MS and SCI subjects but did not meet the 2% frequency criteria when considering only MS subjects: hyperhidrosis, abdominal pain, muscle tightness, abnormal dreams, muscle spasticity, fecal incontinence, and decreased appetite. The following AEs met the 2% frequency criteria for MS subjects but not for MS and SCI subjects combined: joint sprain, blood cholesterol increased, coordination abnormal, viral infection, blood CPK increased, pruritis, ecchymosis, fungal infection, migraine, hypercholesterolemia, and white blood cell count increased.

Treatment Emergent AEs in ≥ 2% of Fampridine SR Subjects, MS Trials

AE Preferred Term	**% (n)**	**AE Preferred Term**	**% (n)**
Urinary tract infection	27.5% (252)	Pyrexia	3.6% (33)
Fall	25.8% (237)	Skin laceration	3.6% (33)
Multiple sclerosis relapse	21.3% (195)	Shoulder pain	3.5% (32)
Asthenia	19.4% (178)	Myalgia	3.4% (31)
Insomnia	18.1% (166)	Pain	3.4% (31)
Headache	17.6% (161)	Pharyngolarygeal pain	3.1% (28)
Dizziness	17.3% (159)	Cough	3.1% (28)
Fatigue	15.3% (140)	Gastroenteritis viral	3.1% (28)
Nausea	14.7% (135)	Burning sensation	2.9% (27)
Upper resp tract inf	13.4% (123)	Hypertension	2.9% (27)
Paresthesia	11.5% (105)	Vertigo	2.9% (27)
Back pain	11% (101)	Micturition urgency	2.8% (26)
Pain in extremity	10.7% (98)	Bronchitis	2.8% (26)
Arthralgia	10.7% (98)	Gait disturbance	2.8% (26)
Edema peripheral	9.7% (89)	Joint swelling	2.7% (25)
Balance disorder	9.6% (88)	Joint sprain	2.7% (25)
Contusion	9.1% (83)	Neck pain	2.6% (24)
Muscle spasms	8.3% (76)	Dyspnea	2.6% (24)
Nasopharyngitis	8.1% (74)	Cellulitis	2.6% (24)
Depression	7.3% (67)	Blood Cholesterol inc	2.5% (23)
Constipation	6.9% (63)	Coordination abnormal	2.5% (23)
Diarrhea	6.5% (60)	Viral infection	2.5% (23)
Hypoaesthesia	6.5% (60)	Blood CPK increased	2.4% (22)
Tremor	6.4%% (59)	Pruritis	2.4% (22)
Difficulty walking	5.7% (52)	Vision blurred	2.4% (22)
Influenza	4.8% (44)	Stomach discomfort	2.3% (21)
Vomiting	4.6% (42)	Abdominal pain upper	2.3% (21)
Anxiety	4.5% (41)	Ecchymosis	2.2% (20)
Sinusitis	4.5% (41)	Fungal infection	2.2% (20)
Rash	4.5% (41)	Chest pain	2.1% (19)
Urinary incontinence	4.4% (40)	Erythema	2.1% (19)
Musculoskeletal stiffness	4.3% (39)	Migraine	2.1% (19)
Dyspepsia	3.8% (35)	Hypercholesterolemia	2% (18)
Pollakiuria	3.8% (35)	White blood cell count inc	2% (18)
Cystitis	3.8% (35)	Trigeminal neuralgia	2% (18)
Excoriation	3.7% (34)		

AEs from Adequate and Well Controlled MS Trials
ISS Table 22.2.2a summarized treatment emergent AEs for the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204). In these trials, 86.4% (438/507) of Fampridine SR subjects experienced one or more AEs compared to 73.5% (175/238) of placebo subjects. The table below identified the AEs occurring in at least 1% of Fampridine SR subjects and that occurred more frequently compared to placebo. I highlighted those AEs that were at least 2 times more frequent among Fampridine SR subjects compared to placebo.

Treatment Emergent AEs Occurring in ≥1% of Fampridine SR Subjects and More Frequently Compared to Placebo, Adequate and Well Controlled MS Trials

AE Preferred term	Placebo (n=238)	Fampridine Total (n=507)	Fampridine 10mg bid (n=400)	Fampridine 15mg bid (n=50)	Fampridine 20mg bid (n=57)
Subjects with 1 or more AEs	73.5% (175)	86.4% (438)	84.8% (339)	94% (47)	91.2% (52)
Urinary tract infection	9.2% (22)	14.3% (72)	14.5% (58)	10% (5)	15.8% (9)
Insomnia	3.8% (9)	10.5% (53)	9.3% (37)	18% (9)	12.3% (7)
Dizziness	4.2% (10)	9.5% (48)	7.8% (31)	20% (10)	12.3% (7)
Headache	4.2% (10)	8.9% (45)	7.5% (30)	14% (7)	14% (8)
Asthenia	4.2% (10)	8.7% (44)	8.3% (33)	18% (9)	3.5% (2)
Nausea	2.5% (6)	7.7% (39)	7% (28)	10% (5)	10.5% (6)
Fatigue	4.6% (11)	7.5% (38)	6.5% (26)	14% (7)	8.8% (5)
Multiple sclerosis relapse	3.8% (9)	6.5% (33)	5.3% (21)	8% (4)	14% (8)
Balance disorder	1.3% (3)	6.3% (32)	5.8% (23)	8% (4)	8.8% (5)
Paresthesia	3.4% (8)	5.7% (29)	4.8% (19)	6% (3)	12.3% (7)
Back pain	2.1% (5)	5.3% (27)	5.5% (22)	4% (2)	5.3% (3)
Muscle spasms	3.4% (8)	4.1% (21)	3.8% (15)	6% (3)	5.3% (3)
Nasopharyngitis	2.9% (7)	4.1% (21)	4.3% (17)	6% (3)	1.8% (1)
Constipation	2.1% (5)	3.7% (19)	3.5% (14)	4% (2)	5.3% (3)
Diarrhea	2.5% (6)	2.8% (14)	2.5% (10)	6% (3)	1.8% (1)
Difficulty walking	1.3% (3)	2.8% (14)	2.5% (10)	0	7% (4)
Pharyngolaryngeal pain	0.8% (2)	2.6% (13)	2.3% (9)	4% (2)	3.5% (2)
Gastroenteritis viral	1.7% (4)	2.4% (12)	2% (8)	2% (1)	5.3% (3)
Pollakiuria	0.8% (2)	2.4% (12)	2% (8)	2% (1)	5.3% (3)
Vomiting	0.4% (1)	2.4% (12)	2% (8)	6% (3)	1.8% (1)
Pyrexia	0.8% (2)	2.2% (11)	1.8% (7)	4% (2)	3.5% (2)
Rash	0.8% (2)	2.2% (11)	1.8% (7)	2% (1)	5.3% (3)
Anxiety	0.4% (1)	2% (10)	1.8% (7)	2% (1)	3.5% (2)
Cough	1.7% (4)	2% (10)	1.5% (6)	2% (1)	5.3% (3)
Tremor	0	2% (10)	1.3% (5)	0	8.8% (5)
Dyspepsia	0.8% (2)	1.8% (9)	2% (8)	2% (1)	0

Influenza	0	1.8% (9)	2.3% (9)	0	0
Muscle spasticity	1.7% (4)	1.8% (9)	2% (8)	0	1.8% (1)
Pain	0.8% (2)	1.8% (9)	1.3% (5)	6% (3)	1.8% (1)
WBC urine positive	0.8% (2)	1.8% (9)	1.8% (7)	2% (1)	1.8% (1)
Depression	0.8% (2)	1.6% (8)	1.3% (5)	2% (1)	3.5% (2)
Urinary incontinence	0	1.6% (8)	1.3% (5)	0	5.3% (3)
Viral infection	0.4% (1)	1.6% (8)	1.5% (6)	4% (2)	0
Abdominal pain	0.4% (1)	1.4% (7)	1.3% (5)	0	3.5% (2)
Cystitis	0.8% (2)	1.4% (7)	1.5% (6)	2% (1)	0
Dyspnea	0	1.4% (7)	1% (4)	4% (2)	1.8% (1)
Joint swelling	1.3% (3)	1.4% (7)	1.3% (5)	2% (1)	1.8% (1)
Myalgia	0.8% (2)	1.4% (7)	1% (4)	4% (2)	1.8% (1)
Pruritis	0.4% (1)	1.4% (7)	1.5% (6)	2% (1)	0
Shoulder pain	1.3% (3)	1.4% (7)	1.3% (5)	2% (1)	1.8% (1)
Skin laceration	0	1.4% (7)	1.3% (5)	2% (1)	1.8% (1)
Back injury	0.8% (2)	1% (5)	1.3% (5)	0	0
Bronchitis	0.8% (2)	1% (5)	0.8% (3)	4% (2)	0
Chest pain	0.4% (1)	1% (5)	0.8% (3)	2% (1)	1.8% (1)
Diplopia	0.4% (1)	1% (5)	0.8% (3)	2% (1)	1.8% (1)
Dry mouth	0.8% (2)	1% (5)	0.8% (3)	0	3.5% (2)
Hypertension	0.4% (1)	1% (5)	0.8% (3)	0	3.5% (2)
Muscular weakness	0	1% (5)	0.3% (1)	2% (1)	5.3% (3)
Neck pain	0.8% (2)	1% (5)	1% (4)	0	1.8% (1)
Sensory disturbance	0.4% (1)	1% (5)	1% (4)	0	1.8% (1)
Stomach discomfort	0.8% (2)	1% (5)	0.8% (3)	2% (1)	1.8% (1)
Vertigo	0.4% (1)	1% (5)	1% (4)	0	1.8% (1)
WBC count decreased	0.4% (1)	1% (5)	1% (4)	2% (1)	0

From ISS Table 22.2.2a

AEs from Adequate and Well Controlled SCI Trials
ISS Table 22.3.2a summarized TEAEs for the adequate and well controlled SCI trials (SCI-F201, SCI-F301, and SCI-F302). In these trials, 90.6% (251/277) of Fampridine SR subjects experienced one or more AEs compared to 86.5% (198/229) of placebo subjects. The table below identifies the AEs occurring in at least 5% of Fampridine SR subjects and that occurred more frequently compared to placebo. I highlighted those AEs that were at least 2 times more frequent among fampridine subjects compared to placebo.

Treatment Emergent AEs in ≥5% of Fampridine SR Subjects and that Occurred More Frequently Compared to Placebo, Adequate and Well Controlled SCI Trials

AE Preferred term	Placebo (n=229)	Fampridine Total (n=277)	Fampridine 25mg bid (n=247)	Fampridine 40mg bid (n=30)
Subjects with 1 or more AEs	86.5% (198)	90.6% (251)	89.5% (247)	100% (30)
Urinary tract infection	16.6% (38)	26% (72)	25.5% (63)	30% (9)
Dizziness	2.6% (6)	15.9% (44)	13% (32)	40% (12)
Constipation	9.2% (21)	15.5% (43)	14.6% (36)	23.3% (7)

Headache	10% (23)	14.1% (39)	11.7% (29)	33.3% (10)
Muscle spasticity	12.2% (28)	13.7% (38)	10.5% (26)	40% (12)
Insomnia	4.8% (11)	13.4% (37)	10.9% (27)	33.3% (10)
Nausea	6.6% (15)	11.9% 933)	10.1% (25)	26.7% (8)
Paresthesia	3.9% (9)	11.6% (32)	10.1% (25)	23.3% (7)
Back pain	4.8% (11)	9.4% (26)	8.1% (20)	20% (6)
Fatigue	5.2% (12)	7.9% (22)	6.1% (15)	23.3% (7)
Anxiety	1.3% (3)	7.6% (21)	4.9% (12)	30% (9)
Pain in extremity	4.8% (11)	7.6% (21)	6.9% (17)	13.3% (4)
Asthenia	3.5% (8)	7.2% (20)	4.9% (12)	26.7% (8)
Musculoskeletal stiffness	4.8% (11)	6.1% (17)	4.9% (12)	16.7% (5)
Abdominal pain	0.9% (2)	5.4% (15)	4% (10)	16.7% (5)
Decreased appetite	1.3% (3)	5.1% (14)	3.6% (9)	16.7% (5)

From Table 22.3.2a

Additional Analyses of Select Common AEs

Dizziness
Dizziness was commonly reported by subjects treated with Fampridine SR, was more common among Fampridine SR treated subjects than placebo subjects, and the risk for dizziness increased with dose. In MS adequate and well controlled trials, 48 Fampridine SR subjects experienced dizziness. The median time to onset of dizziness for these 48 subjects was 12 days (range 1 to 107 days). The median duration of dizziness for these subjects was 7 days (range 0-76 days). The majority of verbatim terms coded to the preferred term dizziness were “dizziness” and “lightheadedness”. The outcome for dizziness was reported as resolved for 43 subjects, not resolved for 4 subjects, and outcome was not provided for 1 subject. The vital sign data did not suggest meaningful Fampridine SR -related declines in blood pressure (see below) that would explain the increased risk of dizziness. In the adequate and well controlled MS trials, no subjects had AEs of blood pressure decreased and there did not appear to be a meaningful increase in risk for syncope among Fampridine SR subjects (0.4%, 2/507) compared to placebo (0/237).

I assessed the relationship between dizziness and other select AEs (contusion, balance disorder, difficulty walking, fall, fracture, and skin laceration) by comparing the percentage of MS patients from the adequate and well controlled trials with dizziness and a given AE, with the expected risk assuming that the events were independent (Risk of dizziness x Risk for studied AE).

For the examined events, the observed risk for co-occurrence in subjects of AEs exceeded the expected (presuming independence) for balance disorder and dizziness and fall and dizziness but after examining the individual cases, many of the events di not occur contemporaneously. In the adequate and well controlled trials, 8 fampridine patients (1.6%) experienced both dizziness and balance disorder compared to an expected risk of 0.6% (risk of dizziness 9.5% x risk of balance disorder 6.3%). An

examination of the data set for the 8 patients with dizziness and balance disorder demonstrated that the AEs were contemporaneous for only 4 of the 8 cases.

In the MS adequate and well controlled trials, 3.2% (n=16) of fampridine patients experienced both dizziness and fall compared to an expected risk of 1.5% (risk of dizziness 9.5% x risk of fall 15.6%). An examination of the data set for the 16 patients with dizziness and fall demonstrated that the AEs were contemporaneous for only 5 of the 16 cases.

Insomnia
Insomnia was commonly reported by subjects treated with Fampridine SR, was more common among Fampridine SR treated subjects than placebo subjects, and the risk for insomnia increased with dose. In MS adequate and well controlled trials, 53 Fampridine SR subjects experienced insomnia. The median time to onset of insomnia for these 53 subjects was 15 days (range 1 to 106 days). The median duration of insomnia for the 31 subjects with a day of resolution in the data set was 26 days (range 0-110 days).

Asthenia
Asthenia was commonly reported by subjects treated with Fampridine SR, was more common among Fampridine SR treated subjects than placebo subjects, and the risk for asthenia increased with Fampridine SR dose. In MS adequate and well controlled trials, 44 Fampridine SR subjects experienced asthenia. The median time to onset of asthenia for these 44 subjects was 44.5 days (range 1 to 121 days). The median duration of asthenia for the 26 subjects with a day of resolution in the data set was 14 days (range 0-43 days).

7.4.2 Laboratory Findings

Chemistry
Mean Change Results Adequate and Well Controlled MS Trials
ISS table 33.2.2 provided mean change from baseline chemistry results from the adequate and well controlled MS trials. The mean changes from baseline in these trials were generally similar for Fampridine SR and placebo subjects. Fampridine SR subjects experienced a larger mean increase in LDH compared to placebo subjects. The difference between Fampridine SR and placebo in mean change for LDH appeared to be driven by a large decline in one placebo subject (-1013). The median change from baseline for LDH was 3 for placebo and 1 for fampridine.

I summarize the mean change from baseline chemistry results below.

Chemistry Mean Change from Baseline to Days 43 through 119, Adequate and Well Controlled MS Trials

Analyte	Placebo (n=238)	Fampridine SR (n=507)

Albumin (g/L)	-1.11 (n=230)	-1.39 (n=487)
Alkaline Phosphatase (U/L)	2.92 (n=233)	2.44 (n=491)
Blood Urea Nitrogen (mmol/L)	0.52 (n=233)	0.51 (n=491)
Calcium (mmol/L)	-0.01 (n=233)	-0.03 (n=491)
Cholesterol (mmol/L)	0.14 (n=233)	0.02 (n=491)
Triglycerides (mmol/L)	0.2 (n=233)	0.17 (n=491)
Creatine Kinase (µmol/L)	14.68 (n=233)	13.23 (n=489)
Creatinine (µmol/L)	2.28 (n=233)	3.67 (n=491)
Glucose (mmol/L)	0.17 (n=233)	0.04 (n=491)
Lactate dehydrogenase (U/L)	0.97 (n=233)	4.3 (n=489)
Phosphorus (mmol/L)	-0.09 (n=233)	-0.1 (n=488)
Potassium (mmol/L)	0.12 (n=233)	0.11 (0.38)
AST (U/L)	2.32 (233)	2.13 (n=490)
ALT (U/L)	4.48 (n=119)	3.6 (n=121)
Bilirubin (µmol/L)	0.52 (n=233)	0.63 (n=491)
Sodium (mmol/L)	-0.6 (n=233)	-0.65 (n=490)
Urate (mmol/L)	0.01 (n=233)	0.01 (n=491)
Protein (g/L)	-1.85 (n=233)	-2.41 (n=491)

Mean Change Results Adequate and Well Controlled SCI Trials
ISS table 33.3.2 summarized the mean change from baseline chemistry lab results. As with the MS trials, the mean changes from baseline were similar for Fampridine SR and placebo in the adequate and well controlled SCI trials. For LDH, Fampridine SR subjects experienced a mean increase from baseline at days 43-119 of 7.29 compared to 2.76 for placebo. The median increase in LDH for Fampridine SR subjects was 6 compared to 3 for placebo subjects.

Outlier Results Adequate and Well Controlled MS Trials
ISS table 42.2.2 identified the percentage of subjects with chemistry lab results that met clinically significant cutoff criteria. The chemistry outlier results were generally similar for Fampridine SR and placebo subjects. There was an almost 2 fold higher risk for phosphorus outliers for Fampridine SR subjects compared to placebo subjects. I summarize those results below.

Chemistry Outlier Results, Adequate and Well Controlled MS Trials

Analyte (outlier criteria)	Placebo (n=238)	Fampridine SR (n=507)
Albumin (<=25 or >=65g/L)	0/233	0/499
Alkaline Phosphatase (>=3xULN)	0/236	0/503
BUN (>=10.7mmol/L)	1.7% (4/236)	1.4% (7/503)
Calcium (<1.75 or>3.0 mmol/L)	0/236	0/503
Cholesterol (>7.77 mmol/L)	2.5% (6/236)	1.8% (9/503)

Creatine Phosphokinase (>=3xULN)	1.7% (4/236)	0.6% (3/501)
Creatinine (>=176.8 µmol/L)	0/236	0.4% (2/503)
Glucose (<2.775 or >13.875mmol/L)	0.8% (2/236)	1% (5/503)
Lactate dehydrogenase (>=3xULN)	0/236	0/501
Phosphorus (<0.646 or >1.615 mmol/L)	2.5% (6/236)	4.6% (23/501)
Potassium (<3.0 or >5.0mmol/L)	1.3% (3/236)	1.2% (6/501)
AST (>3xULN)	0/236	0/502
ALT (>3xULN)	0/121	0/123
Bilirubin (>=34.2µmol/L)	0/236	0.4% (2/503)
Sodium (<130 or >150mmol/L)	0/236	1.2% (6/502)

Using the submitted lab data sets, I determined that for phosphorus outliers, all 6 placebo subjects had high outlier results (2.5%, 6/238) and that 19 Fampridine SR subjects had high outliers (3.7%, 19/507) making this apparent disparity less concerning.

For the two Fampridine SR subjects with bilirubin elevations, the significant lab results (2.4mg/dL and 2.6mg/dL) represented declines from the baseline results for these subjects.

For the Fampridine SR subjects with sodium outlier results, 3 had elevations and 3 had declines.

Outlier Results Adequate and Well Controlled SCI Trials
ISS table 42.3.2 identified the percentage of subjects with chemistry lab results that were outside the normal range. The chemistry outlier results in the adequate and well controlled SCI trials were generally similar to those in the MS trials summarized above. As with the MS trials, there was a higher risk for sodium outlier results among Fampridine SR subjects (1.1%, 3/264) compared to placebo subjects (0/216). The finding in MS trials of an increased risk for phosphorus result outliers among Fampridine SR subjects was not replicated in the SCI trials where the outlier risk for Fampridine SR was 1.1% (3/264) and for placebo was 3.2% (7/216).

Additional Analyses
To look for evidence of Fampridine SR-related hepatotoxicity, I asked Acorda to identify and summarize all cases of liver injury as defined by ALT or AST >3x ULN AND total bilirubin >2x ULN. Acorda reported that no cases in their database met those criteria. For the adequate and well controlled MS trials, no subjects with normal ALT at baseline had an on treatment ALT>3x ULN, with normal AST at baseline had an on treatment AST>3x ULN, or with normal bilirubin at baseline had on treatment bilirubin>1.5x ULN.

In the SCI adequate and well controlled trials, one Fampridine SR subject (ACD-002580) with a normal AST at baseline had an AST result on treatment that was >3xULN (result was <5x ULN). One Fampridine SR subject (ACD-000583) with a normal bilirubin at baseline had an on treatment bilirubin >1.5xULN (result was <2xULN) (Response to reviewer questions 3/13/09).

Hematology

Mean Change Results Adequate and Well Controlled MS Trials
ISS table 34.2.2 provided mean change from baseline hematology results from the adequate and well controlled MS trials. The mean changes from baseline in these trials were generally similar for Fampridine SR and placebo. I summarize results from that table below.

Hematology Mean Change from Baseline to Days 43 through 119, Adequate and Well Controlled MS Trials

Analyte	Placebo (n=238)	Fampridine SR (n=507)
Basophils (10^9/L)	0.01 (n=231)	0.01 (n=486)
Eosinophils (10^9/L)	0.02 (n=231)	0.03 (n=486)
Hematocrit (%)	-1.17 (n=231)	-1.49 (n=487)
Hemoglobin (g/L)	-2.3 (n=231)	-2.97 (n=488)
Lymphocytes (10^9/L)	-0.14 (n=231)	0.02 (n=485)
Monocytes (10^9/L)	0.05 (n=231)	0.05 (n=486)
Neutrophils (10^9/L)	-0.47 (n=231)	-0.46 (n=486)
Platelets (10^9/L)	5.95 (n=231)	6.55 (n=487)
Leukocytes (10^9/L)	-0.15 (n=231)	-0.13 (n=488)

Mean Change Results Adequate and Well Controlled SCI Trials
ISS table 34.3.2 summarized the mean change from baseline hematology lab results. As with the MS trials, the mean changes from baseline in the adequate and well controlled SCI trials were similar for Fampridine SR and placebo. In the SCI trials, for lab results between days 43 and 119, Fampridine SR subjects experienced a slight mean increase in platelet count (4.66) compared to a slight decline (-1.79) for placebo subjects.

Outlier Results Adequate and Well Controlled MS Trials
ISS table 43.2.2 identified the percentage of subjects with hematology lab results that met clinically significant outlier cutoff criteria. The hematology outlier results were generally similar for Fampridine SR and placebo subjects. Fampridine SR subjects did have a higher risk for low hemoglobin outlier results compared to placebo. I summarize those results below.

Hematology Outlier Results, Adequate and Well Controlled MS Trials

Analyte (outlier criteria)	Placebo (n=238)	Fampridine SR (n=507)
Basophils >=0.4)	0/234	0.4% (2/500)
Eosinophils (>=0.7)	0.9% (2/234)	0.8% (4/500)
Hematocrit (<=37% males, <=32% females)	2.1% (5/234)	2.4% (12/500)
Hemoglobin (<=115 males, <=95 females)	0.4% (1/234)	1.2% (6/501)
Lymphocytes (<=0.5 or >=4.5))	2.1% (5/234)	3.8% (19/499)
Monocytes (>=1.5)	0.4% (1/234)	0.4% (2/500)
Neutrophils (<=1.0)	0.9% (2/234)	0.2% (1/500)
Platelets (<=75 or >=700 k/mm3)	(0/234)	0.4% (2/500)
Leukocytes (<=2.8 or >=16 k/mm3)	3.0% (7/234)	3.2% (16/501)

Outlier Results Adequate and Well Controlled SCI Trials
ISS table 43.3.2 identified the percentage of subjects with hematology lab results that were outside the normal range. The hematology outlier results in the adequate and well controlled SCI trials were generally similar to those in the MS trials summarized above. The finding in MS trials of an increased risk for low hemoglobin result outliers among Fampridine SR subjects was not replicated in the SCI trials where the low hemoglobin outlier risk for placebo was 2.8% (6/212) and for Fampridine SR was 0.8% (2/257).

Urinalysis

Adequate and Well Controlled MS Trials
ISS table 44.2.2 provided urinalysis results from the adequate and well controlled MS trials. There were no meaningful differences in risk for urinalysis test results when comparing Fampridine SR and placebo subjects. Despite the increased risk of UTI among Fampridine SR study subjects, they did not appear to have an increase in urinary leukocytes results. Acorda reported that 25.1% (126/502) Fampridine SR subjects had leucocytes on UA compared to 30.9% (73/236) of placebo subjects.

Adequate and Well Controlled SCI Trials
ISS table 44.3.2 provided outlier urinalysis results from the adequate and well controlled SCI trials. There were no meaningful differences in outlier risk for urinalysis test results when comparing Fampridine SR and placebo subjects. As with the MS study results, UA results from SCI subjects did not support AE data suggesting an increased risk of UTI with Fampridine SR. Acorda reported that 41% (83/202) of Fampridine SR subjects had positive leukocyte esterase results compared to 42% (78/187) of placebo subjects.

7.4.3 Vital Signs

Mean Change Results Adequate and Well Controlled MS Trials
ISS table 45.2.2 summarized the mean change from baseline vital sign results from the adequate and well controlled MS trials. There did not appear to be notable mean change vital sign differences between Fampridine SR and placebo in these trials. I provide those results below

Vital Sign Change from Baseline to Days 43 through 70, Adequate and Well Controlled MS Trials

Analyte	Placebo (n=238)	Fampridine (n=507)
Diastolic BP (mmHg)	0.06 (n=226)	-0.61 (n=462)
Diastolic BP upright-supine (mmHg)	0.83 (n=109)	-0.41 (n=341)
Systolic BP (mmHg)	0.95 (n=226)	-0.68 (n=463)
Systolic BP upright-supine (mmHg)	0.29 (n=109)	-0.33 (n=342)
Temperature (C)	0.21 (n=226)	0.04 (n=461)
Weight (kg)*	-0.05 (n=237)	-0.35 (n=504)

*Uses Final Assessment data

Mean Change Results Adequate and Well Controlled SCI Trials
ISS table 45.3.2 summarized the mean change from baseline vital sign results from the adequate and well controlled SCI trials. There did not appear to be notable mean change vital sign differences between Fampridine SR and placebo in these trials.

Outlier Vital Sign Results Adequate and Well Controlled MS Trials
ISS table 47.2.2 identified the percentage of subjects with vital sign results that met clinically significant outlier cutoff criteria during the adequate and well controlled MS trials. Fampridine SR subjects had a slightly higher risk for low SBP outliers (<90mm Hg and decrease >=20mmHg) compared to placebo (fampridine 4.5%, 23/507; placebo 2.5%, 6/238). The risk for low SBP outlier by fampridine dose was 3.3% (13/400) for 10mg bid; 12% (6/50) for 15mg bid; and 7% (4/57) for 20mg bid. The risks for the remaining vital sign outliers were similar for Fampridine SR and placebo.

Outlier Vital Sign Results Adequate and Well Controlled SCI Trials
ISS table 47.3.2 identified the percentage of subjects with vital sign results that met clinically significant outlier cutoff criteria during the adequate and well controlled SCI trials. The risks for vital sign outliers were similar for Fampridine SR and placebo.
In these trials, the risk for low SBP outliers among placebo subjects was 16.4% (37/226) was slightly higher when compared to fampridine subjects (14.8%, 41/277).

7.4.4 Electrocardiograms (ECGs)

Mean Change Results Adequate and Well Controlled MS Trials
ECGs were performed in the MS adequate and well controlled trials at screening, during study treatment and following treatment. Acorda summarized ECG results from the Adequate and Well Controlled MS Trials in ISS table 48.2.2. For the mean change analyses, I focused on the change from screen to days 43-119, an on-treatment period that included the greatest number of study participants. In the table below, I summarize these results. There did not appear to meaningful differences when comparing Fampridine SR and placebo subjects in these trials.

ECG Mean Change from Screening to Days 43 through 119, Adequate and Well Controlled MS Trials

ECG Parameter	Placebo (n=238)	Fampridine SR (n=507)
Heart rate (beats per minute)	-1.6 (n=234)	-1.16 (n=492)
PR interval (msec)	3.21 (233)	2.51 (492)
QRS interval (msec)	2.43 (234)	2.34 (492)
QT Interval (msec)	2.15 (234)	3.10 (492)
QTcF (msec)	3.10 (234)	4.06 (492)

From ISS table 48.2.2

Mean Change Results Adequate and Well Controlled SCI Trials
Acorda summarized ECG results from the Adequate and Well Controlled SCI Trials in ISS table 48.3.2. The reported mean changes from these trials were generally small and similar for Fampridine SR and placebo subjects.

Outlier ECG Results Adequate and Well Controlled MS Trials
ISS table 50.2.2 identified the percentage of subjects with ECG results that met clinically significant outlier cutoff criteria during the adequate and well controlled MS trials. The risks for the ECG outliers were similar for Fampridine SR and placebo. I summarize that data below.

ECG Outlier Results, Adequate and Well Controlled MS Trials

ECG Parameter	Outlier criteria	Placebo (n=238)	Fampridine SR (n=507)
Heart rate	<50 bpm and >25% change from baseline	0/236	0.2% (1/505)
PR	>=200 msec and >25% change from baseline	0/235	1/505
QRS	>=100 msec and >25% change from baseline	1.7% (4/236)	1% (5/505)
QTc	>=450 msec	3.4% (8/236)	2% (10/505)
QT	>=450 msec	2.5% (6/236)	2.8% (14/505)

QTc	>=500 msec	0.4% (1/236)	0/505
QT	>=500 msec	0.4% (1/236)	0/505

From ISS table 50.2.2

Outlier ECG Results Adequate and Well Controlled SCI Trials
ISS table 50.3.1 identified the percentage of subjects with ECG results that met clinically significant outlier cutoff criteria during the adequate and well controlled SCI trials. The risks for ECG outliers were similar for Fampridine SR and placebo.

QTc Increases from Baseline Adequate and Well Controlled MS Trials
In the adequate and well controlled MS trials, 3.8% (9/236) of placebo subjects experienced an increase in QTc from baseline of >30-<=60 msec compared to 4.6% (23/505) Fampridine SR subjects. In these same trials, 0.4% (1/236) of placebo subjects experienced an increase in QTc of >60 msec compared to no (0/505) Fampridine SR subjects (ISS table 51.2.2).

QTc Increases from Baseline Adequate and Well Controlled SCI Trials
In the adequate and well controlled SCI trials, 5.9% (13/221) of placebo subjects experienced an increase in QTc from baseline of >30-<=60 msec compared to 10.4% (28/270) Fampridine SR subjects. In these same trials, 1.8% (4/221) of placebo subjects experienced an increase in QTc of >60 msec compared to 3% (8/270) Fampridine SR subjects (ISS table 51.3.2).

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT Trial
As part of the development program, Acorda conducted a thorough QT trial to examine the effect of Fampridine SR on cardiac repolarization. The thorough QT trial was reviewed by CDER's Interdisiciplinary Review Team in a memo dated 12/04/08. The review team found no significant QT prolongation with either the 10mg or the 30mg Fampridine SR dose. The team found that "The largest upper bounds of the 2-sided 90% CI for the mean difference between Fampridine SR (10 mg and 30 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance." The team reported that assay sensitivity was established in this study by detection of QT prolongation with moxifloxacin.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In proposed labeling for Fampridine SR, Acorda recommends only the 10mg bid dose for MS patients. Because patients will only be treated with one dose, information about dose dependency for AEs has limited utility for prescribers. Assessment of dose dependency may provide supplemental evidence of causal relationships between Fampridine SR and AEs.

The adequate and well controlled clinical trials for MS included Fampridine SR doses of 10mg bid, 15mg bid, and 20mg bid. Acorda reported evidence of a dose response for AEs leading to discontinuation from MS controlled trials. Acorda noted that 8.8% (5/57) of subjects randomized to Fampridine SR 20mg bid discontinued for AEs compared to 2.8% (11/400) randomized to 10mg bid, 2% (1/50) randomized to 15mg bid and 2% (5/238) randomized to placebo. This dose relationship was especially evident for Nervous System Disorder AEs leading to discontinuation where 8.8% (5/57) of MS subjects randomized to Fampridine SR 20mg bid discontinued for Nervous System Disorder AEs compared to 2% (1/50) randomized to 15mg bid, 1.3% (5/400) randomized to 10mg bid and 0.8% (2/238) randomized to placebo (ISS Table 27.2.2).

In the following table I identify those common Fampridine SR -related AEs (>=2% of fampridine MS subjects and more common than placebo) that also showed evidence of a dose response (risk higher among the 15mg bid and 20mg bid dose groups compared to the 10mg bid dose group).

Common Fampridine SR -related AEs (≥2% of Fampridine SR MS subjects and More Frequent than Placebo) that Showed Evidence of a Dose Response

AE Preferred term	Placebo (n=238)	Fampridine SR Total (n=507)	Fampridine SR10mg bid (n=400)	Fampridine SR15mg bid (n=50)	Fampridine SR 20mg bid (n=57)
Subjects with 1 or more AEs	73.5% (175)	86.4% (438)	84.8% (339)	94% (47)	91.2% (52)
Insomnia	3.8% (9)	10.5% (53)	9.3% (37)	18% (9)	12.3% (7)
Dizziness	4.2% (10)	9.5% (48)	7.8% (31)	20% (10)	12.3% (7)
Headache	4.2% (10)	8.9% (45)	7.5% (30)	14% (7)	14% (8)
Nausea	2.5% (6)	7.7% (39)	7% (28)	10% (5)	10.5% (6)
Fatigue	4.6% (11)	7.5% (38)	6.5% (26)	14% (7)	8.8% (5)
Multiple sclerosis relapse	3.8% (9)	6.5% (33)	5.3% (21)	8% (4)	14% (8)
Balance disorder	1.3% (3)	6.3% (32)	5.8% (23)	8% (4)	8.8% (5)
Paresthesia	3.4% (8)	5.7% (29)	4.8% (19)	6% (3)	12.3% (7)
Muscle spasms	3.4% (8)	4.1% (21)	3.8% (15)	6% (3)	5.3% (3)
Constipation	2.1% (5)	3.7% (19)	3.5% (14)	4% (2)	5.3% (3)
Pharyngolaryngeal pain	0.8% (2)	2.6% (13)	2.3% (9)	4% (2)	3.5% (2)

Pyrexia	0.8% (2)	2.2% (11)	1.8% (7)	4% (2)	3.5% (2)
Rash	0.8% (2)	2.2% (11)	1.8% (7)	2% (1)	5.3% (3)
Anxiety	0.4% (1)	2% (10)	1.8% (7)	2% (1)	3.5% (2)
Cough	1.7% (4)	2% (10)	1.5% (6)	2% (1)	5.3% (3)

From ISS Table 22.2.2a

AEs leading to discontinuation also displayed a dose response in the SCI adequate and well controlled trials. The adequate and well controlled SCI trials included Fampridine SR doses of 25mg bid and 40 mg bid. In these trials, 33.3% (10/30) of 40mg bid subjects discontinued for AEs compared to 15.4% (38/247) of 25mg bid subjects and 3.5% (8/229) of placebo subjects. Dose response for body system AEs leading to discontinuation was seen with Gastrointestinal disorders (40mg bid 13.3%, 20mg bid 3.2%, placebo 0.4%), General disorders (40mg bid 20%, 20mg bid 4%, placebo 0.9%), Nervous system disorders (40mg bid 33.3%, 20mg bid 9.3%, placebo 1.3%), and Psychiatric disorders (40mg bid 20%, 20mg bid 4.9%, placebo 0.4%) (ISS table 27.3.2).

In the following table I identify those common Fampridine SR -related AEs (>=5% of fampridine SCI subjects and more common than placebo) that also showed evidence of a dose response (risk higher among the 40mg bid dose group compared to the 25mg bid dose group).

Common Fampridine SR AEs (>=5% of Fampridine SR SCI subjects and More Frequent than Placebo) with Evidence of Dose Response

AE Preferred term	Placebo (n=229)	Fampridine Total (n=277)	Fampridine 25mg bid (n=247)	Fampridine 40mg bid (n=30)
Subjects with 1 or more AEs	86.5% (198)	90.6% (251)	89.5% (247)	100% (30)
Urinary tract infection	16.6% (38)	26% (72)	25.5% (63)	30% (9)
Dizziness	2.6% (6)	15.9% (44)	13% (32)	40% (12)
Constipation	9.2% (21)	15.5% (43)	14.6% (36)	23.3% (7)
Headache	10% (23)	14.1% (39)	11.7% (29)	33.3% (10)
Muscle spasticity	12.2% (28)	13.7% (38)	10.5% (26)	40% (12)
Insomnia	4.8% (11)	13.4% (37)	10.9% (27)	33.3% (10)
Nausea	6.6% (15)	11.9% 933)	10.1% (25)	26.7% (8)
Paresthesia	3.9% (9)	11.6% (32)	10.1% (25)	23.3% (7)
Back pain	4.8% (11)	9.4% (26)	8.1% (20)	20% (6)
Fatigue	5.2% (12)	7.9% (22)	6.1% (15)	23.3% (7)
Anxiety	1.3% (3)	7.6% (21)	4.9% (12)	30% (9)
Pain in extremity	4.8% (11)	7.6% (21)	6.9% (17)	13.3% (4)
Asthenia	3.5% (8)	7.2% (20)	4.9% (12)	26.7% (8)
Musculoskeletal stiffness	4.8% (11)	6.1% (17)	4.9% (12)	16.7% (5)
Abdominal pain	0.9% (2)	5.4% (15)	4% (10)	16.7% (5)
Decreased appetite	1.3% (3)	5.1% (14)	3.6% (9)	16.7% (5)

From Table 22.3.2a

7.5.2 Time Dependency for Adverse Events

Examination of time dependency for select AEs is included above in section 7.4.1.

7.5.3 Drug-Demographic Interactions

Acorda analyzed TEAE data from adequate and well controlled MS trials for evidence of demographic interactions. Using all TEAEs, Acorda provided AE risks stratified by treatment and by the following demographic factors: sex, age (<=45 years, 46-<65 years, and >65 years), and race (Caucasian, non-Caucasian). From these data I calculated relative risks. I provide the results of this analysis below. For sex and age, there did not appear to be important differences in risk for all AEs. The relative risk for TEAEs was higher among non-Caucasians than Caucasians, based on a small number of non-Caucasian subjects in these trials (non Caucasian fampridine subjects n=37). This difference was driven by lower TEAE risks among the non-Caucasian placebo subjects.

TEAE Risk from Adequate and Well Controlled MS Trials Stratified by Demographic Factors

Demographic factors	Percent (number) with any TEAE		Relative Risk
Sex	Fampridine (n=507)	Placebo (n=238)	
Male	80.4% (123)	68.1% (64)	1.2
Female	89.0% (315)	77.1% (111)	1.2
Age			
<=45	87.1% (101)	70.8% (46)	1.2
46-<=65	86.6% (316)	76.1% (118)	1.1
>65	80.8% (21)	61.1% (11)	1.3
Race			
Caucasian	86.4% (406)	76.9% (166)	1.1
Non-Caucasian	86.5% (32)	40.9% (9)	2.1

From Table 18, Summary of Clinical Safety, p.66.

In addition to the demographic analysis using all TEAEs summarized above, Acorda also provided tables (32.2.2.1, 32.2.2.2, and 32.2.2.3) that stratified each individual TEAEs by sex, age, and race. I used these tables to look for demographic interactions, focusing on TEAEs that occurred in at least 5% of Fampridine SR subjects and at least twice as commonly compared to placebo in the adequate and well controlled MS trials.

Sex
The relative risk for insomnia was higher for females (RR 2.9; Fampridine SR 12.1%, placebo 4.2%) than males (RR 2.0; Fampridine SR 6.5%, placebo 3.2%). Females also had a higher relative risk for balance disorder TEAEs (RR 5.4; Fampridine SR 7.6%, placebo 1.4%) compared to males (RR 3.0; fampridine 3.3%, placebo 1.1%). For the

remaining TEAEs occurring in at least 5% of Fampridine SR subjects and at least twice as commonly compared to placebo, the RR for males and females were similar.

Age
The oldest age group (>65 years) included only 26 Fampridine SR subjects and 18 placebo subjects, offering insufficient information to support firm conclusions about TEAE risks in this age group. The relative risk for insomnia was higher for subjects aged <45 years (RR 3.6; Fampridine SR 11.2%, placebo 3.1%) than 45-<=65 years (RR 2.5; Fampridine SR 9.6%, placebo 3.9%). Subjects 45->=65 years had a higher relative risk for back pain (RR 3.6; Fampridine SR 4.7%, placebo 1.3%) compared to subjects <45 years (RR 1.9; Fampridine SR 6.0%, placebo 3.1%). For the remaining TEAEs occurring in at least 5% of Fampridine SR subjects and at least twice as commonly compared to placebo, the RR for subjects aged <45 years and subjects 45->=65 years were similar.

Race
Most subjects (470 of 507 Fampridine SR and 216 of 238 placebo subjects) in the adequate and well controlled MS trials were Caucasian, limiting the ability to detect differences in relative risk for TEAEs when stratified by race.

7.5.4 Drug-Disease Interactions

Acorda looked for evidence of drug-disease interaction among MS patients with and without abnormal renal function. Acorda considered patients with a creatinine clearance <=80ml/min[2] as having abnormal renal function (Response to Reviewer questions 7/14/09). For all TEAEs, the relative risk for subjects with abnormal renal function (RR 1.35; Fampridine SR 89.8%, placebo 66.7%) was higher than the relative risk for subjects with normal renal function (RR 1.14; fampridine 85.6%, placebo 74.9%). For the TEAEs occurring in at least 5% of Fampridine SR subjects and at least twice as commonly compared to placebo, Fampridine SR subjects with abnormal renal function had higher risks and RR for nausea, balance disorder, dizziness, and insomnia. I provide those data below.

TEAE Risk Stratified by Renal Function

	Normal Renal Function			Abnormal Renal Function		
AE	Fampridine N=409	Placebo N=199	RR	Fampridine N=98	Placebo N=39	RR
Nausea	7.1% (29)	2.5% (5)	2.8	10.2% (10)	2.6% (1)	3.9
Balance disorder	4.2% (17)	1.5% (3)	2.8	15.3% (15)	0	-

[2] Estimated creatinine clearance (in mL/minute) was calculated using the Cockcroft/Gault formulae:
(140-Age)*Weight / (72 * Serum Creatinine) for males;
(140-Age) * Weight * 0.85 / (72 * Serum Creatinine) for females

Dizziness	8.8% (36)	5% (10)	1.8	12.2% (12)	0	-
Insomnia	9% (37)	4% (8)	2.3	16.3% (16)	2.6% (1)	6.3

Data from ISS table 32.2.2.4

7.5.5 Drug-Drug Interactions

Using 3 broad categories of concomitant medications, Acorda looked for evidence of drug-drug interactions among MS patients. Acorda classified subjects as to whether they were taking immune modulators, antispasticity medications, or antidepressants. For the 3 classes of concomitant medications studied, there did not appear to be important differences in relative risks for all TEAEs when comparing subjects taking the medications to those not taking the medication (Data from Summary of Clinical Safety, Table 18, pp.66-7).

For those TEAEs occurring in at least 5% of Fampridine SR subjects and at least twice as commonly compared to placebo in the adequate and well controlled MS trials, the relative risks comparing Fampridine SR and placebo subjects for those taking immune modulators were either similar to or lower than the relative risks for those not taking immune modulators, suggesting no interaction for these events (Data from ISS table 32.2.2.5).

When considering antispasticity medications and TEAEs that occurred in at least 5% of Fampridine SR subjects and at least twice as commonly compared to placebo in the adequate and well controlled MS trials, balance disorder was the only TEAE where the RR among subjects using antispasticity medications (RR 6.1; Fampridine SR 4.9%, placebo 0.8%) was notably higher compared to subjects not using antispasticity medications (RR 4.4; Fampridine SR 7.9%, placebo 1.8%)(Data from ISS table 32.2.2.6).

For antidepressants, when examining the TEAEs that occurred in at least 5% of Fampridine SR subjects and at least twice as commonly compared to placebo in the adequate and well controlled MS trials, back pain was the only TEAE where the risk among subjects using antidepressants (Fampridine SR 7.2%, placebo 0) was notably different compared to subjects not using antidepressants (RR 1.4; Fampridine SR 4.5%, placebo 3.2%) (Data from ISS table 32.2.2.7)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Acorda did not include in their NDA submission a review of human cancer diagnoses in the Fampridine SR development program, so I requested a listing of all malignancies diagnosed during Fampridine SR clinical trials. The listing provided by Acorda included the diagnoses that were present in the AE dataset, captured under the body system category "Neoplasms benign, malignant, and unspecified (incl cysts and polyps)". Therefore, I relied on the AE dataset and relevant ISS tables to review cancers diagnosed during the Fampridine SR clinical trials.

In the integrated safety database, the risk for "Neoplasms benign, malignant, and unspecified (incl cysts and polyps)" body system category TEAEs was 2.1% (45/2115). The malignant neoplasms that occurred in more than one subject were basal cell cancer (n=10), squamous cell cancer (n=5), breast cancer (n=3), and prostate cancer (n=2) (ISS Table 22.0).

In the adequate and well controlled MS trials, there were 3 AEs under the "Neoplasms benign, malignant, and unspecified (incl cysts and polyps)" body system category. All three events (breast cancer, lentigo, and leiomyoma) occurred in Fampridine SR subjects (ISS Table 22.2.2a). In the adequate and well controlled SCI trials, there were 2 TEAEs under the "Neoplasms benign, malignant, and unspecified (incl cysts and polyps)" body system category. Both events (lip and or oral cavity cancer, lipoma) occurred in Fampridine SR subjects (ISS Table 22.3.2a).

The clinical trial database did not suggest a relationship between Fampridine SR and cancer diagnoses. Due to the relatively short duration of exposure and follow up, the Fampridine SR safety database is not expected to support a robust assessment of human carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

Acorda did not identify any human pregnancy concerns in their submission. They report that adequate and well controlled trials in pregnant women have not been performed. A search of the AE data set identified one Fampridine SR subject (MS-F203EXT, 03004) with a pregnancy. This 35 year old female had her first dose of study medication in this trial on 2/8/06. On 4/14/07 she stopped Fampridine SR due to pregnancy. On 4/25/07 she had an ultrasound that estimated the gestational age at 7 weeks and 3 days. The patient delivered a full term female on 11/27/07. No birth defects were noted.

Acorda reported that the safety of Fampridine SR in infants of breast feeding women is not known.

7.6.3 Pediatrics and Assessment of Effects on Growth

Acorda did not study the use of Fampridine SR in pediatric subjects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Acorda identified 2 patients in clinical trials that took doses of Fampridine SR that were either higher or more frequent than prescribed. I summarize those events below.

> Subject #07019 from study MS-F202, a 47 year old woman with secondary progressive MS (EDSS=4), experienced a partial complex seizure after taking a double dose of 20 mg Fampridine-SR (total 40 mg) to compensate for a previously missed dose. She was found by her father who reported that she was unresponsive with automatisms, and later was confused, tremulous, and diaphoretic. She did not recall the event and did not seek medical treatment. On the day of the overdose (Study Visit 7, 49 days on double blind treatment) the patient's plasma fampridine concentration at approximately 4.5 hours post dose was 79.0 ng/mL and she experienced a partial complex seizure of moderate severity 4 hours later. With reassurances of future compliance, the patient was allowed to continue in the trial but, ten days later, she again took two doses within a short period of time. She became confused for about an hour and was discontinued from the study at that point. An EEG performed 1 week later showed "bilaterally independent mild temporal slowing with some rare sharp waves, more prominent on the left than on the right, indicative of a tendency for partial seizures." Concomitant medications included betaseron and lexapro.

> Subject #10 from trial SCI-F301, a 36 year old male spinal cord injury patient experienced an adverse event of accidental study drug overdose. This event was associated with AEs of confusion, disorientation, and sweating. None of these AEs were considered SAEs. The subject recovered on the same date that the overdose was reported. This overdose resulted from the patient mistakenly taking two 25mg tablets at the same time (Response to Reviewer Questions 7/14/09).

In addition to the Fampridine SR clinical trial data, Acorda summarized overdose reports for 4-aminopyridine that they identified from the medical literature (ISS, pp. 367-9). The highest identified 4-aminopyridine overdose came from a report by Smeets and Kunst which described a 22 year old who ingested 2 to 4 grams of 4-aminopyridine (not clear

over what period of time). The patient's serum level was 355µg/L (represents approximately 7 times the therapeutic level, time following ingestion not reported). Reported symptoms included seizures, vomiting, agitation, tachypnea, diaphoresis, incontinence, hypertension (160/104 mmHg), transient right bundle branch block, PVCs, and accelerated idioventricular rhythm. He was treated with gastric lavage, activated charcoal, diazepam, iv fluids, clonazepam, lidocaine, phenytoin, and nitroprusside and recovered in 2 days.

A case series by Burton et al reported on 4 MS patients who ingested 4-aminopyridine doses approximately 10 times higher than expected (due to improper compounding). The authors reported that these patients experienced unusual sensory and behavioral symptoms, and status epilepticus. Three patients recovered but continued to have increased neurological disability when examined 1 year after the event. The fourth patient died following a prolonged hospitalization.

Other symptoms reported in patients who ingested overdoses of 4-aminopyridine include tremulousness, dystonia, choreoathetoid-type movements, fixed stare, facial paralysis, delirium, slurred speech, disorientation, and hypothermia.

In a publication by Badrudddin, Menon, and Reder, the authors suggested that 4-aminopyridine toxicity mimics autoimmune-mediated limbic encephalitis. The authors described a 22 year old male with MS who ingested 30 10mg tablets of 4-aminopyridine. The patient initially experienced hypertension (209/108mm Hg) and runs of supraventricular tachycardia. An EEG showed diffuse polyspike and spike-wave discharges that normalized over time (the patient did not experience seizures). An echocardiogram demonstrated hypokinesis with an EF of 24%. MRI showed bilateral medial temporal lobe hyperintensity on T2 and fluid attenuated inversion recovery that did not enhance with gadolinium. CSF had normal cell count, protein, and glucose, but contained oligoclonal bands. Five days after overdose, the patient was awake but had minimal awareness of the examiner and did not speak and his strength was described as 1/5. His CPK peaked at 494U/L. His speech was described as hypophonic and neuropsychiatric evaluation found memory loss. His EF improved to 57% and an endomyocardial biopsy on day 12 did not find inflammation, fibrosis, or toxic inclusion. Nerve conduction velocities were normal, EMG was consistent with myopathy, and muscle biopsy showed mild focal endomysial inflammation with normal blood vessels and architecture. The patient's speech and language and ambulation improved over time. An MRI at 4 months after the overdose no longer showed signal abnormalities. At one year, the patient continued to have difficulty with short term memory and learning new tasks. The authors felt that the cognitive deficits, abulia, and temporal lobe lesions in this patient were similar to the findings in patients with HSV or paraneoplastic limbic encephalitis. The authors explained that in limbic encephalitis, antibodies bind potassium channels of peripheral and central neurons. The authors suggested that blockade by 4-aminopyridine of Kv1.1 and other Kv1 subtypes in the hippocampus and limbic circuit was likely and could explain the amnesia, bradykinesia and impaired visual

learning seen in their overdose patient. The authors felt that the cardiac dysfunction, EMG abnormalities, and skeletal muscle findings were due to a reversible toxic myopathy.[3]

Drug Abuse Potential

Acorda reports that there are no indications of abuse potential with Fampridine SR. Acorda notes that preclinical studies indicate that Fampridine SR specifically binds potassium channels and not other receptors or channels and that aside from toxicological effects at higher doses animal studies did not find behavioral effects. In healthy human subjects, fampridine produced dizziness, nausea, and insomnia but did not produce stimulant or depressant effects on mood. In the development program trials, no reports of euphoric mood were seen in the 993 MS and SCI controlled trial patients or the 1029 MS patients overall. Acorda did note that there were 3 reports of euphoric mood among 704 uncontrolled trial SCI patients and 2 reports in non patient safety population (n=382). Acorda also found few cases of hallucination (4/1029 MS patients, 5/704 SCI patients, 1/384 non patient population). Lastly, Acorda reports that the overdose reports are mostly accidental. Acorda noted that there are a few literature reports of attempted abuse of fampridine, but these were one-time events, based on uninformed exploratory behavior, that produced acute negative side effects and did not lead to repeated attempts (response to Reviewer Questions 7/14/09).

Withdrawal

In Fampridine SR trials, investigators recorded AEs that occurred following discontinuation of study medication, allowing for an assessment of withdrawal effects. ISS table 22.1.1c summarized the TEAEs occurring after cessation of trial medication for all MS and SCI trials. The TEAEs reported by at least 1% of MS and SCI patients following discontinuation of Fampridine SR were urinary tract infection (2.6%, 40/1510), fall (2.2%, 33/1510), asthenia (1.6%, 24/1510), fatigue (1.6%, 24/1510), muscle spasticity (1.2%, 18/1510), muscle spasms (1.1%, 16/1510), and MS relapse (1.1%, 16/1510).

In table 22.2.2c, Acorda summarized TEAEs occurring after stopping study medication for the adequate and well controlled MS trials. The post treatment TEAEs that occurred in at least 1% of Fampridine SR subjects and more frequently when compared to placebo were urinary tract infection (Fampridine SR 3.2%, 16/507, placebo 0.8%, 2/238), MS relapse (Fampridine SR 2.2%, 11/507, placebo 0.4%, 1/238), asthenia (Fampridine SR 2.2%, 11/507, placebo 0.4%, 1/238), fatigue (Fampridine SR 2%, 10/507, placebo 0), balance disorder (Fampridine SR 1.4%, 7/507, placebo 0), difficulty in walking (Fampridine SR 1.2%, 6/507, placebo 0), muscle spasticity (Fampridine SR 1%, 5/507, placebo 0.8%, 2/238), cystitis (Fampridine SR 1%, 5/507, placebo 0), and upper respiratory tract infection (Fampridine SR 1%, 5/507, placebo 0.8%, 2/238).

3 Badruddin A, Menon RS, Reder AT. 4-Aminopyridine Toxcity Mimics Autoimmune-Mediated Limbic Encephalitis, Neurology 2009;72;1100-1101.

In table 22.3.2c, Acorda summarized AEs occurring after stopping study medication for the adequate and well controlled SCI trials. The post treatment TEAEs that occurred in at least 1% of Fampridine SR subjects and more frequently when compared to placebo were constipation (Fampridine SR 1.8%, 5/277, placebo 0.9%, 2/229), fatigue (Fampridine SR 1.4%, 4/277, placebo 0), oedema peripheral (Fampridine SR 1.1%, 3/277, placebo 0.4%, 1/229), urinary tract infection (Fampridine SR 2.9%, 8/277, placebo 1.3%, 3/229), muscle spasms (Fampridine SR 2.2%, 6/277, placebo 1.7%, 4/229), musculoskeletal stiffness (Fampridine SR 1.4%, 4/277, placebo 0.9%, 2/229), somnolence (Fampridine SR 1.1%, 3/277, placebo 0), anxiety (Fampridine SR 1.1%, 3/277, placebo 0.4%, 1/229), and decubitus ulcer (Fampridine SR 1.1%, 3/277, placebo 0).

The AE data set included one study subject with an AE of drug withdrawal. This 53 year old male spinal cord injury patient participating in study SCI F201EXT experienced “excess sweating –assoc. withdrawal symptom”. This event was classified as severe but was not an SAE. The recorded outcome of this event was “resolved”.

7.7 Additional Submissions / Safety Issues

There were no data from submissions other than those noted above.

8 Postmarket Experience

Fampridine is not approved for use and therefore there are no available post marketing data.

9 Appendicies

9.1 Advisory Committee Meeting

On 10/14/09, the Peripheral and Central Nervous System Advisory Committee met to discuss the Fampridine SR NDA. As part of the discussion of safety, the committee addressed special circumstances for the use of fampridine SR and considered specific required testing.

The committee stated that EEG testing should not be required prior to treatment of fampridine. Despite using screening EEGs in the fampridine clinical trials, the committee felt that there was a lack of data on EEG as a screening tool for seizure in MS patients. Furthermore, the committee felt that the available data from the use of EEG in healthy populations (i.e. pilot applicants) suggested that EEG has low predictive value for

seizure and that false positive EEG results could lead to unnecessary, expensive, and potentially harmful follow up restrictions, testing, and treatments.

Given that fampridine is predominately cleared unchanged via renal excretion and that the evidence suggests a narrow therapeutic window for seizure, the committee felt that fampridine should be contraindicated in moderate and severe renal insufficiency and that patients should be tested (estimated creatinine clearance) prior to the use of fampridine SR.

Given the dose relationship for seizure and other adverse events, the committee also recommended that Acorda study use of lower dosages of fampridine. The committee felt that these lower dosage studies could be performed after approval.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GERARD A BOEHM
10/26/2009

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10/26/2009